



FROM THE EXPERTS IN ENDOCRINOLOGY

2026 ENDOCRINE CASE MANAGEMENT: MEET THE PROFESSOR

FROM THE EXPERTS IN ENDOCRINOLOGY

ENDO 2026
MEET THE PROFESSOR



ENDOCRINE

CASE MANAGEMENT



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Clinical Practice Chair, ENDO 2026
Ana Paula Abreu Metzger, MD, PhD

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ENDO 2026 OVERVIEW



OVERVIEW

Endocrine Case Management: Meet the Professor is designed to provide physicians with a concise, high-quality review of 40 common and rare endocrine disorders to help you keep your practice current. It features case-based clinical vignettes and rationales written by experts across all areas of endocrinology, diabetes, and metabolism.

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Endocrine Case Management: Meet the Professor enables learners to assess their knowledge of all aspects of endocrinology, diabetes, and metabolism.

Upon completion of this educational activity, learners will be able to:

- Recognize the clinical manifestations of endocrine and metabolic disorders and select among current diagnostic, management, and therapeutic options.
- Identify risk factors for endocrine and metabolic disorders and develop prevention strategies.
- Evaluate endocrine and metabolic manifestations of systemic disorders.
- Use existing resources on clinical guidelines and treatment recommendations for endocrine and related metabolic disorders to guide diagnosis and treatment.

TARGET AUDIENCE

Endocrine Case Management: Meet the Professor provides case-based education for clinicians seeking to improve patient care.

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COMMON ABBREVIATIONS IN MEET THE PROFESSOR

ACTH = corticotropin	FSH = follicle-stimulating hormone	NPH insulin = neutral protamine Hagedorn insulin
ACE inhibitor = angiotensin-converting enzyme inhibitor	GH = growth hormone	PCSK9 inhibitor = proprotein convertase subtilisin/kexin 9 inhibitor
ALT = alanine aminotransferase	GHRH = growth hormone-releasing hormone	PET = positron emission tomography
AST = aspartate aminotransferase	GLP-1 receptor agonist = glucagonlike peptide 1 receptor agonist	PSA = prostate-specific antigen
BMI = body mass index	GnRH = gonadotropin-releasing hormone	PTH = parathyroid hormone
CNS = central nervous system	hCG = human chorionic gonadotropin	PTHrP = parathyroid hormone-related protein
CT = computed tomography	HDL = high-density lipoprotein	SGLT-2 inhibitor = sodium-glucose cotransporter 2 inhibitor
DHEA = dehydroepiandrosterone	HIV = human immunodeficiency virus	SHBG = sex hormone-binding globulin
DHEA-S = dehydroepiandrosterone sulfate	HMG-CoA reductase inhibitor = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor	T₃ = triiodothyronine
DNA = deoxyribonucleic acid	IGF-1 = insulinlike growth factor 1	T₄ = thyroxine
DPP-4 inhibitor = dipeptidyl-peptidase 4 inhibitor	LDL = low-density lipoprotein	TPO antibodies = thyroperoxidase antibodies
DXA = dual-energy x-ray absorptiometry	LH = luteinizing hormone	TRH = thyrotropin-releasing hormone
FDA = Food and Drug Administration	MCV = mean corpuscular volume	TRAb = TSH-receptor antibodies
FGF-23 = fibroblast growth factor 23	MIBG = <i>meta</i> -iodobenzylguanidine	TSH = thyrotropin
FNA = fine-needle aspiration	MRI = magnetic resonance imaging	VLDL = very low-density lipoprotein



ADIPOSE TISSUE, APPETITE, OBESITY, AND LIPIDS

Lipedema at the Intersection of Endocrinology and Adipose Biology

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Recognize lipedema as a distinct disorder of loose connective tissue under the umbrella of obesity, distinct from vascular disease–related lymphedema.
 - Describe endocrinology and adipose biology relevant to the development and future treatment of lipedema.
 - Discuss current and emerging treatment options to reduce morbidity from lipedema.
-

Significance of the Clinical Problem

What Is Lipedema?

Lipedema is a chronic disorder of subcutaneous adipose tissue characterized by disproportionate fat accumulation in the limbs (usually the legs, sometimes the arms) and almost exclusively affects women. First described in 1940 by Allen and Hines, lipedema is distinct from general obesity and lymphedema, with morbidity decreasing quality of life.^{1,2} In lipedema, excessive fat deposition causes symmetric enlargement of the legs and/or arms, often presenting as a columnlike leg shape, while hands and feet remain unaffected until late stages. A hallmark is that the affected fat

tissue is painful to palpation and prone to bruising with minor trauma, indicative of capillary fragility. Unlike common obesity, the fat in lipedema is diet-resistant, meaning patients often report little improvement in limb size even after significant weight loss. This can help distinguish lipedema from simple obesity. Importantly, lipedema fat deposition is usually bilateral and symmetric, differentiating it from lymphedema, in which swelling is often unilateral.³ In summary, lipedema is recognized as a loose connective tissue disease of fat, involving nodular, fibrotic fat accumulation on the hips, buttocks, and limbs, arising in the context of hormonal and developmental triggers (eg, puberty), and causing progressive disproportionate limb enlargement with pain.

Diagnostic Criteria

The diagnosis of lipedema is clinical, based on a thorough patient history, characteristic physical exam findings, and exclusion of other conditions. Formal diagnostic criteria were established by the US Standard of Care consensus,⁴ which outlined key features for identifying lipedema in practice. There is no specific laboratory test or biomarker for lipedema; instead, clinicians rely on recognizing a constellation of signs and symptoms. Major criteria include: (1) a bilateral, symmetric distribution of abnormal subcutaneous fat, typically affecting the legs (from the hips down to the ankles) and sometimes the arms, with sparing of the feet and hands (producing an

abrupt cutoff or “cuffing” at the ankles or wrists); (2) a negative Stemmer sign, meaning the skin at the base of the toes and fingers can be pinched and lifted (in contrast to lymphedema, where this is usually impossible due to swelling); (3) little or no pitting edema on pressure, at least in early stages (any swelling in lipedema is nonpitting and generally minimal unless lymphatic compromise develops). Additional supportive criteria include pain, tenderness, and easy bruising in the affected fat tissue; patients often report that even slight pressure or minor bumps cause pain and bruising in the legs. Onset or worsening during hormonal changes, such as around puberty or pregnancy, is another common historical clue. Importantly, disproportionate fat distribution is a key feature; the lower body is much more enlarged than the upper body, sometimes accompanied by palpable fat nodules in the subcutis. In contrast, the trunk remains comparatively slender, and the feet are not swollen, distinguishing lipedema from generalized obesity or lymphedema. Patients typically do not experience significant

improvement in limb size with calorie restriction or exercise (diet-resistant fat), which can aid in diagnosis. Clinical examination may also reveal textural changes in the skin, depending on the stage of the disease. In early stages, the skin may feel rubbery with fine nodularity, progressing to larger nodules and an irregular “mattress-like” texture in later stages as fibrotic nodules form. Formal staging systems grade the skin and tissue nodularity: stage 1, smooth skin, soft nodules; stage 2, uneven skin surface, large nodules (apple-to walnut-sized), fat thickening, and fibrosis; stage 3, large extrusion of fat tissue, indurated masses and lobules of fat; and stage 4, sometimes used to denote lipedema with accompanying lymphedema (lipo-lymphedema), as shown in the *Figure*. Additionally, lipedema is classified by type based on regional distribution: type I: buttocks/hips; type II: buttocks to the knees; type III: down to the ankles; type IV: arms; type V: calves. These staging classifications, illustrated in the *Figure*, help document the extent of disease for clinical and research purposes.

Figure. Stages of Lipedema According to Progression of Fat Accumulation and Changes to Skin and Lymphatic System



Adapted from the Lipedema Foundation, lipedema.org

[Color—Print (Color Gallery page CG3) or web & ePub editions]

Prevalence

Lipedema is believed to be far more common than historically recognized, affecting a substantial percentage of the female population. Precise prevalence figures remain uncertain because of underdiagnosis and past confusion with obesity, but recent estimates suggest that roughly 11% (up to nearly 1 in 9) of adult women worldwide may have lipedema. In specific settings, even higher rates have been reported; for example, a German literature review reported that 6% to 8% of women in the general population could have lipedema, and 15% to 19% of women seen in specialty vascular clinics were diagnosed with lipedema.⁵ In contrast, lipedema is exceedingly rare in men, with only isolated case reports, usually in men with extreme hormonal disorders, such as testosterone deficiency or estrogen excess, or liver disease.

Practice Gaps

- Lipedema is common among women seeking care for weight management or vascular medicine.
- Lipedema does not respond to medical or surgical weight-loss interventions. Cornerstones of therapy include compression and, in advanced cases, plastic surgery to remove affected adipose tissue.
- As a disorder of loose connective tissue, including adipose tissue, lipedema has important hormonal connections to its development and pathophysiology that endocrinologists should be aware of.

Discussion

Pathophysiology

The pathophysiology of lipedema is complex and generally involves abnormal expansion of subcutaneous adipose tissue, associated microvascular changes influenced by genetic predisposition, and environmental cues. Conceptually, this pathophysiology can be

organized into vascular, endocrine, and adipose components, among others, for the purposes of this chapter.

Vascular Component

Despite the “edema” suffix, lipedema does not involve fluid accumulation in early stages. Unlike lymphedema, the hallmark of lipedema is disproportionate, symmetric accumulation of painful adipose tissue in the upper or lower extremities. Feet, hands, trunk, neck, and head are not affected.⁴ The Stemmer sign, in which the examiner cannot pinch the skin of the toes, is negative in lipedema. By contrast, lymphedema stems from impaired lymphatic capillary drainage, often begins distally in the feet, and tends to be asymmetric. In this context, lipedema is often considered to have relative lymphatic sparing and minimal edema in early stages. The microvasculature in lipedema is compromised, leading to easy bruising and increased vascular permeability in fat, both of which indicate a microangiopathic state. Leaky capillaries may lead to bruising after minor trauma, as well as to pressure, heaviness, and pain on palpation. In later stages, secondary lymphedema can coexist, resulting in the condition termed lipo-lymphedema. The International Lipedema Consensus of 2020 proposed that chronic inflammation and tissue hypoxia in the enlarging fat are likely causes of the pain in lipedema, rather than fluid edema per se.⁴ This insight shifts the treatment focus in lipedema beyond purely decompressive therapies toward anti-inflammatory and antiobesity strategies, among others. Vascular and lymphatic factors in lipedema appear secondary to adipose pathology but can progress as the disease advances, underscoring the importance of vascular and lymphatic care in later disease stages.

Endocrine Component

Lipedema development is closely associated with hormonal changes across the female life course.⁶ Lipedema often appears or worsens during periods of major hormonal flux and weight change, classically

at puberty, sometimes during pregnancy, and frequently at menopause. A common hypothesis is that lipedema may be linked to estrogen surges during these transitions. Research suggests that lipedema adipose tissue may have an abnormal estrogen profile, including an imbalance in estrogen receptor alpha ($ER\alpha$) and beta ($ER\beta$) levels. Estrogen promotes the accumulation of adipose tissue in the gluteofemoral distribution, consistent with the lipedema fat distribution. One study reported reduced $ER\alpha$ and increased $ER\beta$ in adipose tissue from patients with lipedema, which could promote lipid accumulation in lower-body depots.⁷ Progesterone and androgen levels have also been implicated in pregnancy and the menopausal transition, respectively, but direct evidence is lacking. Hormonal triggers are central to when lipedema manifests and flares, making it a quintessential example of an endocrine-influenced adipose disorder. Future research focused on the molecular endocrinology of lipedema could reveal targeted ways to interrupt this hormonal trigger cycle.

Adipose Component

At its core, lipedema is a disorder of adipose tissue within loose connective tissue. Adipocytes play the starring role in pathophysiology, with both hypertrophic and hyperplastic changes documented.^{7,8} Histological studies of lipedema fat have demonstrated adipocyte hypertrophy (enlarged fat cells) and adipocyte hyperplasia (increased number of fat cells) in the affected areas.⁹ These observations imply that the subcutaneous tissue in lipedema can expand markedly in volume, partly by each fat cell storing more lipid and swelling, and partly by recruiting or differentiating new fat cells. This contrasts with typical obesity, where hypertrophy tends to predominate.¹⁰ Lipedema fat often forms a nodular texture; microscopically, nodules of fibrotic connective tissue surround groups of adipocytes, especially in later stages. Notably, in early-stage lipedema, there may be relatively little fibrosis; the skin remains soft, and the fat, although nodular, is not hardened. Consequently, stage 1 lipedema skin feels smooth even though underlying fat nodules

can be palpated like small peas. As the condition progresses to stages 2 and 3, fibrosis increases in the subcutis: collagen deposition and scarlike tissue form around larger clumps of fat, causing the overlying skin to indent and dimple (mimicking cellulite, but more extreme). By stage 3, sizable lobules of fat develop, suspended by fibrous septa, leading to deforming overhangs of tissue around the knees or arms. Despite fibrosis of the fat in lipedema, skin elasticity often remains relatively good (until very advanced disease), which is why compression and surgery can achieve good skin retraction. Importantly, pure lipedema (stages 1-3) does not cause the dermal fibrosis or peau d'orange texture seen in lymphedema. The skin of lipedema, aside from the nodules underneath, can be pinchable and is not woody or indurated. Only when lymphedema overlaps does the skin begin to thicken. Another component of the adipose tissue change is the inflammatory cell infiltrate. Research indicates that lipedema fat depots have a distinct immune cell composition compared to both normal and obesity-related fat. There is evidence of a higher proportion of M2 macrophages (alternatively activated, anti-inflammatory macrophages) in lipedema tissue, whereas obesity-related fat tends to have more proinflammatory M1 macrophages. This M2 predominance might sound counterintuitive, since lipedema is painful (one would expect inflammation to cause pain), but it likely reflects a chronic, unresolved state of tissue remodeling. Some theorize that the pain in lipedema is due to nerve irritation within the expanding fat. Indeed, hypoxia and mild inflammation can sensitize nerves. One hypothesis is that as fat hypertrophies, small nerve fibers in the tissue are stretched or compressed, leading to a neuropathic pain element. There is also evidence of abnormal adipose stem-cell function in lipedema. A study found that adipose-derived stem cells from patients with lipedema have impaired adipogenesis in vitro and altered adipokine expression. Intriguingly, these differences potentially could serve as biomarkers of lipedema or even as therapeutic targets. From a life-course perspective, once lipedema fat forms,

it tends to be resistant to loss. Calorie restriction or bariatric surgery may reduce overall weight, but often spares the lipedema fat. This suggests a fundamental dysregulation of adipose metabolism in lipedema tissue. Several groups have postulated defects in catecholamine or hormone receptors on lipedema fat cells, or localized adipose hypoxia, leading to insulin resistance in that tissue, but these hypotheses remain under investigation. Finally, unlike fibrotic lymphedema tissue, lipedema adipose tissue remains “soft” fat (especially in the early stages), composed of a loose connective tissue matrix that holds water and fat; thus, the term “loose connective tissue disease” is used for lipedema. The fat is not scarred in the way of postradiation lymphedema tissue; rather, it is an overgrowth of otherwise normal fat cells and supporting stroma. Understanding the adipose component is key to developing treatments; this is why liposuction can dramatically help by physically removing pathological fat cells. In summary, lipedema involves *both* adipocyte hypertrophy and hyperplasia, leading to a significant expansion of subcutaneous fat mass with distinctive nodular fibrosis and inflammatory changes. This adipose pathology, influenced by hormones and genetics, is the central driver of the disease, around which vascular and lymphatic issues revolve.

Treatment Options

There is currently no cure for lipedema, but a variety of treatments can manage symptoms, improve function, and slow disease progression. Optimal care is usually multidisciplinary, combining medical management, nutritional guidance, physical therapies, and sometimes surgery. The overall goals are to reduce pain and swelling, restore mobility, prevent or treat lymphedema, and address the psychosocial impact. As a provider, it is important to set expectations: while treatments can significantly improve quality of life, they typically do not eliminate all lipedema tissue (except through surgical removal), and ongoing maintenance is needed. The main

treatment modalities in the standard of care are discussed in the following sections.

Medical Management

Medical management of lipedema focuses on treating symptoms and related conditions, since no pill or injection can yet specifically remove lipedema fat. Pain management is one aspect. Many patients benefit from analgesics, including nonsteroidal anti-inflammatory agents. If neuropathic pain is suspected, medications such as gabapentin or duloxetine may be tried under physician guidance. Treating coexisting issues is also crucial. For example, if venous insufficiency or varicose veins contribute to edema, medical or interventional treatments for those conditions (such as compression or vein ablation) should be provided. Likewise, managing hypothyroidism, vitamin D deficiency, or any metabolic disorders can help overall tissue health. A cornerstone of medical management is compression therapy, which is considered “medical” because it is prescribed and fitted by health care providers. Consistent use of graduated compression stockings or tights (usually class II, 20–30 mm Hg or higher) helps reduce daily swelling, supports the tissues, and can diminish pain and bruising by limiting microvascular leak. Finding the right compression garment often involves working with a specialist.¹¹ When lipedema overlaps with fluid edema, involvement of a certified lymphedema therapist is extremely beneficial. Certified lymphedema therapists are trained in complete decongestive therapy, which includes manual lymphatic drainage massage, multilayer compression bandaging, exercises, and skin care education.

Surgical Treatment

Another important treatment decision is whether to pursue surgical treatment, specifically, liposuction.⁵ Liposuction for lipedema is generally categorized as a surgical intervention, but because it is one of the few ways to actually remove the pathological fat, it is part of the standard care discussion. Typically, conservative measures are tried for at least 6 to 12 months, and if the patient

still has significant pain or functional limitation, liposuction is considered. Liposuction (ideally using the tumescent technique with microcannulas by surgeons experienced in lipedema) can dramatically improve symptoms: it permanently removes lipedema fat cells, resulting in reduced limb size, improved contour, and often much less pain and bruising. However, liposuction usually requires multiple sessions, as each limb may require 2 to 3 operations staged months apart, and it carries risks typical of any surgery, including fluid shifts and potential lymphatic injury. In experienced hands, liposuction is safe and effective. For many patients with moderate-to-severe lipedema, liposuction is the closest thing to a “definitive” treatment. Some countries, such as Germany, have officially recognized liposuction as part of lipedema therapy and even cover it under insurance in certain cases. In the United States, insurance coverage varies and can be challenging.

Nutrition

There is no single scientifically proven “lipedema diet” at this time. However, several dietary approaches have been advocated by experts and patients, including anti-inflammatory diets, lower-carbohydrate or ketogenic diets, intermittent fasting, gluten-free or allergy-elimination diets, and general weight-loss diets. The common theme across these nutritional strategies is promoting a healthy, balanced diet that the patient can sustain over the long term. In conclusion, nutrition is a cornerstone of lipedema management, aimed at optimizing body composition and reducing inflammation. As Tomada noted,⁶ proper nutrition and weight management can preserve mobility and function and potentially slow disease progression.

After decades of relative neglect, patient advocacy, scientific curiosity, and clinical urgency are driving progress in treating lipedema.¹² Ultimately, the vision for the future is one where lipedema is no longer an “orphan” condition, but a well-characterized medical entity with a range of effective treatments.

Clinical Case Vignettes

Case 1

A 52-year-old woman with class 2 obesity (BMI = 36 kg/m²) presents with worsening bilateral leg swelling. She reports menarche at age 11 and a distant history of leg swelling during puberty. She had difficulty maintaining her weight throughout young adulthood, with “big legs.” Over the past 3 years, the swelling has markedly increased, causing discomfort when putting on clothes and walking. She endorses occasional hot flashes and misses periods every 2 to 3 months.

On physical examination, the patient appears well and has a gynoid pattern of obesity. Palpation of her lower extremities reveals pearl-like nodules along her thighs and hypersensitivity to touch, with associated discomfort.

Laboratory test results are normal, including those from a basic metabolic panel, a complete blood cell count, B-type natriuretic peptide, and measurement of TSH and vitamin B₁₂.

What additional testing (if any) is needed to diagnose lipedema in this patient?

- A. No additional testing needed
- B. Vascular scintigraphy to exclude lymphedema
- C. Coagulation tests
- D. LH, FSH, and estradiol measurement

Answer: A) No additional testing needed

The diagnosis of lipedema relies on a thorough patient history, characteristic physical findings, and the exclusion of other conditions. At this time, there are no specific laboratory findings with diagnostic utility in lipedema, although exciting research is ongoing. Consequently, the lab-based findings listed in Answers B, C, and D can be suggestive but not diagnostic. Vascular scintigraphy is an invasive test that uses nuclear dyes to assess reverse flow in the lymphatic vasculature and can help exclude lymphedema. However, it is not diagnostic of lymphedema.

Case 2

An 18-year-old woman describes a history of larger legs that accelerated during puberty. Despite multiple attempts at diet-induced weight loss and, more recently, medication-induced weight loss, she has been unable to reduce her leg size and has relied on wearing larger boots to conceal her appearance. She now seeks assistance for her enlarged legs, which are limiting her mobility.

On physical examination, the patient's vital signs are within normal limits. Her BMI is 32 kg/m^2 , and she has a gynoid fat distribution with excess skin and dimpling. The Stemmer sign is positive. She has no pain to touch or nodularity in her legs.

Given her likely stage of lipedema, what treatment options should be avoided at this point in her disease course?

- A. Dietary strategies
- B. Complete decongestive therapy
- C. Complete lymphatic therapy
- D. Surgical removal

Answer: D) Surgical removal

This patient likely has class I or II lipedema based on the provided description and is unlikely to have had the disease for more than 10 years, given its onset at puberty. As such, there is ample opportunity to implement a layered approach to prevent progression of lipedema, including dietary strategies (Answer A) and mechanical therapies (eg, complete decongestive therapy [Answer B] and complete lymphatic therapy [Answer C]). Surgical removal (Answer D) of lipedema adipose tissue should be reserved for patients with significant pain or mobility limitations or advanced disease, but guidelines are evolving.

Case 3

A 37-year-old woman with hypertension and type 2 diabetes (hemoglobin $A_{1c} = 6.3\%$ [45 mmol/mol]), controlled for 3 years on metformin, presents to the endocrinology clinic

with concern about leg swelling and oozing. She endorses increased leg mass since menarche and, over the past 4 years, has gained significant weight that has been unresponsive to diuretic treatment or GLP-1 receptor agonist therapy. She now reports pain and painful, pearl-like nodules in her legs, along with oozing from her heels.

On physical examination, the patient has a BMI of 41 kg/m^2 and stable vital signs. Her light-touch sensation remains intact on monofilament testing, and there are mild abrasions on the heel and plantar surfaces with clear fluid oozing. She has excess skin on her thighs and decreased mobility, with difficulty standing from her chair.

Given the patient's presentation with more advanced lipo-lymphedema, what initial therapeutic option should be considered?

- A. Diuretic therapy
- B. Complete decongestive therapy
- C. Another trial of GLP-1 receptor agonist therapy
- D. Surgical removal

Answer: B) Complete decongestive therapy

This patient with lipo-lymphedema would benefit from a layered approach, beginning with mechanical decompression therapies, such as complete decongestive therapy (Answer B), before proceeding to medical or surgical therapies. A vascular medicine evaluation will be important to assess the extent of lymphedema and its effect on lipedema progression. Following vascular evaluation, diuretic therapy (Answer A) may be considered. GLP-1 receptor agonist therapy (Answer C) is generally unable to remove lipedema fat once fibrosis has formed. Surgical removal (Answer D) may be considered after initial mechanical and medical therapies.

Key Learning Points

- Lipedema remains underdiagnosed in the endocrinology community as a disease of loose connective tissue, including adipose tissue,

often overlapping with obesity, characterized by abnormal lower-body fat distribution and pain, and primarily affecting women.

- Lipedema sits at the intersection of endocrinology, given the important hormonal cues to its development, and adipose biology, given the integral role of adipocytes in its development.
- Lipedema does not respond to conventional weight-loss treatments, including GLP-1 receptor agonists or dietary interventions, and treatment often requires a layered approach that includes mechanical, medical, and ultimately surgical interventions.
- Ongoing research aims to identify blood-based and imaging biomarkers that could inform future therapies.

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GLP-1–Based Therapies: Preparing Patients With Obesity for Long-Term Maintenance and Transition

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe practices at each phase of obesity management, namely pretreatment, weight reduction, and chronic care, that promote long-term adherence to an individualized therapeutic plan.
 - Explain how a consensus agreement on treatment goals between a patient and a health care professional can be emphasized throughout all phases of obesity management and used to reinforce adherence to long-term therapy.
 - Describe the need to be flexible with dosing and medication selection as needed for long-term maintenance of weight loss and treatment persistence.
-

Significance of the Clinical Problem

Two peptide medications that act as agonists of nutrient-regulated hormones offer unprecedented efficacy in treating obesity: the GLP-1 receptor agonist semaglutide, approved in 2021, and the dual GLP-1 and GIP agonist tirzepatide, approved in 2023. These medications achieved

an average weight loss of 15% or greater in phase 3 clinical trials, and at this level of weight loss, they effectively prevent and treat a broad array of obesity-related complications and diseases. For this reason, these drugs have been termed second-generation obesity medications.¹ First-generation obesity medications approved on or before 2014 (orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide) have generally produced less than 10% average body weight loss in clinical trials. While first-generation medications remain important in obesity management, they do not achieve weight loss that optimally produces health benefits in many patients.

The advent of second-generation medications greatly facilitates a complications-centric approach to care. The underlying principles are: (a) the treatment of obesity is intended to improve health; (b) obesity-related complications and diseases impair health by reducing quality of life and conferring morbidity and mortality; and (c) the goal and endpoint of therapy is to prevent and treat these complications rather than weight loss of a given number of kilograms per se.^{2,3} The 2016 American Association of Clinical Endocrinology (AACE) obesity treatment guidelines⁴ and all more recent guidelines advocated by professional societies^{5–8} endorse a complications-centric approach to the treatment of obesity as a disease. This requires a diagnosis that includes both

an anthropometric component confirming excess adiposity and a clinical component that involves a medical examination and history to assess the presence and severity of obesity-related complications.^{3,4} This is underscored by the diagnostic term adiposity-based chronic disease (ABCD), advocated by both AACE⁹ and the European Association for the Study of Obesity.¹⁰ ABCD indicates what is being treated (abnormalities in the mass, distribution, and function of adipose tissue) and why it is being treated (a chronic disease that gives rise to complications that impair health). Semaglutide and tirzepatide have been shown to ameliorate complications as primary outcomes in clinical trials, including cardiometabolic disease outcomes such as type 2 diabetes, metabolic dysfunction-associated steatohepatitis, hypertension, dyslipidemia, congestive heart failure due to heart failure with preserved ejection fraction, prevention of major adverse cardiovascular events, and kidney protection against progressive chronic kidney disease, as well as biomechanical complications such as obstructive sleep apnea and osteoarthritis.^{7,8} These medications enable clinicians to engage in effective complications-centric management of their patients and, in this regard, are transformational in the pharmacotherapy of obesity.

Despite the availability of these medications with unprecedented efficacy, the treatment of obesity as a chronic disease (ie, ABCD) remains suboptimal. Our major failing is the large number of patients who do not persist with long-term therapy. In large real-world cohort studies, approximately one-fourth of patients do not fill their prescriptions, and after 1 year, fewer than 50% remain adherent to their medication.^{11,12} Once obesity medications are discontinued, most patients regain weight and lose the health benefits of the weight loss. This occurs because pathophysiological mechanisms involving satiety hormones and their interactions with feeding centers in the brain remain operative and were primarily responsible for generating excess adipose tissue in the first place.¹³ Thus, like other chronic

diseases (eg, diabetes, hypertension), long-term persistence with obesity medications is necessary to derive and sustain optimal patient outcomes.

The reasons for discontinuing obesity medications are multifactorial. However, the foremost cause is the high cost.^{14,15} Second-generation medications remain unavailable to many patients. Only a limited number of insurance companies and self-insured employers provide coverage for obesity care or obesity medications, particularly second-generation GLP-1 receptor agonists. Patients must contend with high copays or out-of-pocket expenses. Other factors are medication-related, including frequent gastrointestinal adverse effects and variable weight-loss response, so that no medication is sufficiently effective in all patients. The availability of obesity medications online without meaningful evaluation and follow-up with a health care professional represents substandard care^{7,8} and makes complications-centric care impossible, since the presence and severity of complications will not be addressed. Procuring these medications online while not under a doctor's care can predispose one to their abuse. Examples include the use of GLP-1-based medications by patients with eating disorders or anorexia nervosa, or by patients who are lean and without disease. Patients deserve better than this. Other issues pertain to the lack of an effective chronic care model for obesity in our health care systems. Foremost is the problem of bias and stigmatization at all levels, including patients, health care professionals, health care systems, and society.¹⁶⁻¹⁸ Internalized weight bias diminishes a patient's ability to act as a care partner, impairs self-efficacy, promotes self-blaming, and reduces adherence to therapeutic plans. Bias among medical professionals against obesity as a treatable disease leads to indifferent engagement of patients, and as a result, health care systems are disinclined to provide infrastructure and access for coordinated multidisciplinary obesity management programs. At the societal level, bias limits effective health messaging and inhibits the development of a built environment and regulatory framework that can ensure the

viability of prepared health care systems, the training of sufficient numbers of health care professionals, and broad access to care.

Practice Gaps

- Patients often do not adhere to long-term pharmacotherapy, and many discontinue obesity medications after 1 year, leading to weight regain and loss of the health benefits of weight loss.
- In some practice settings, particularly those with online access to obesity medications, there can be inadequate evaluation and follow-up of the presence and severity of obesity-related complications, which preclude complications-centric care of obesity as a chronic disease.

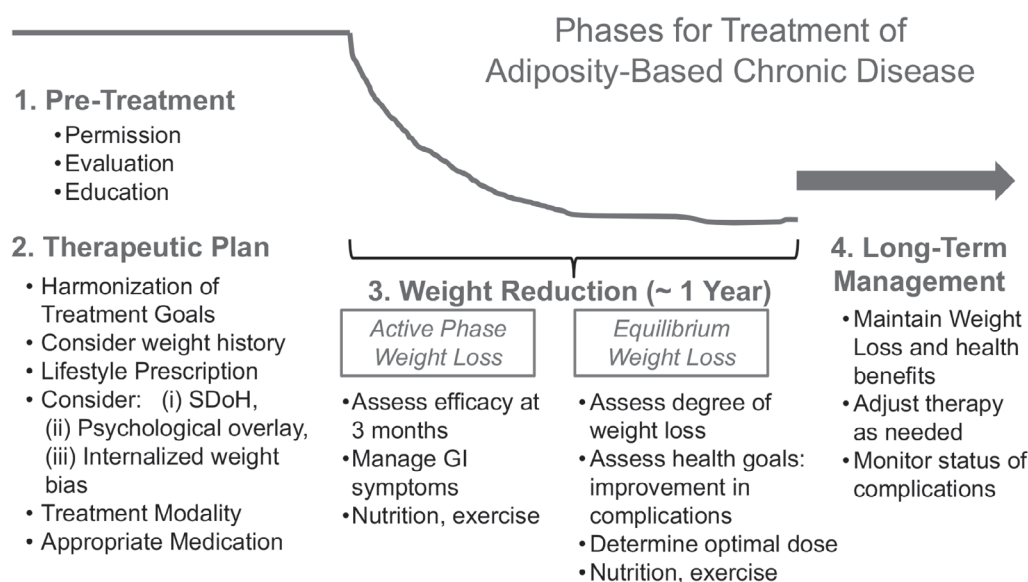
Discussion

Measures to promote long-term medication adherence begin when the patient first enters the clinic and continue throughout the obesity management process, as illustrated in *Figure 1*.

The pretreatment phase requires the patient's permission to discuss weight and the patient's engagement, with empathy and respect. Education is critical to help the patient to understand how excess adiposity affects health, and it should be delivered in a culturally competent manner appropriate to the patient's level of health literacy. The patient should be informed at this early stage that long-term therapy will be needed because obesity is a chronic disease. A full physical examination and history are needed to assess the risk, presence, and severity of obesity-related complications and diseases, enabling evidence-based, complications-centric care.⁸

Developing an individualized treatment plan begins by harmonizing the patient's and the health care professional's treatment goals and desired outcomes. This process meets the patient where they are, in terms of their personal motivation for weight-loss therapy. It also integrates the health care professional's goals of better quality of life, improved health, and the prevention and treatment of obesity-related chronic complications that contribute to morbidity and mortality. This consensus on joint treatment goals and outcomes is then emphasized throughout long-term care and

Figure 1. Phases of Treatment for Adiposity-Based Chronic Disease and Practices That Can Promote Short- and Long-Term Success



[Color—Print (Color Gallery page CG4) or web & ePub editions]

follow-up. The evaluation should also consider the patient's weight history and previous weight-loss attempts, as these factors can influence the treatment plan. Importantly, the therapeutic plan should address the psychological overlay of the disease and the social determinants of health as they apply to each patient.^{8,16} Finally, lifestyle and medical therapy should be tailored together to achieve consensus goals and outcomes, ameliorate the patient's disease complications, and ensure affordability and access to medications. Long-term adherence to obesity medications can be affected by internalized weight bias, psychological disorders, and a therapeutic plan that does not consider social and economic issues.

The weight-reduction phase spans the first year of treatment, encompassing both the acute weight-loss period and the attainment of a lower weight equilibrium. The goal is to establish a feasible intervention plan that meets treatment goals and optimizes outcomes, serving as a prelude to long-term management. Treatment must be sufficiently effective to meet consensus treatment goals and achieve health targets. Modest early-phase weight loss (<5% after 3 months on the treatment dose) can predict inadequate efficacy at 1 year and signal the need to change therapy. The equilibrium level of weight loss should also be sufficient to reverse and prevent complications, and in some patients, may be achieved at a submaximal medication dosage. This phase requires active management of weight loss, addressing gastrointestinal adverse effects, adjusting other medications as needed, and monitoring nutritional status.

The last phase is long-term management, aimed at maintaining weight loss and health benefits throughout the patient's lifetime. Persistence with medication is key, although the dosage and/or medication used for weight-loss maintenance may differ from those used for weight reduction. Monitoring and addressing adverse effects, nutritional status, disease complications, and medication adjustments are needed over time. The actions described at the beginning of treatment and during weight

reduction will predictably promote long-term adherence to therapy. Even so, second-generation medications have been available only since 2021, and we lack data on the management of patients on these drugs over the lifetime. Clearly, our current approach is largely inadequate in maintaining persistence with therapy, whether this relates to the properties of currently available medications, drug costs, adverse effects, widespread bias regarding obesity as a chronic disease, or the structure of our health care systems.¹⁷ Clinicians need to be flexible when needed to address issues that could result in medication discontinuation on an individual patient basis, and some suggestions are described in the following text.

Several aspects of obesity management across all phases of obesity care deserve greater emphasis to promote long-term adherence, including (a) harmonization of treatment goals, (b) weight-loss plateau, (c) psychological overlay, (d) social determinants of health, (e) gastrointestinal adverse events, and (f) long-term pharmacotherapy.

For successful long-term management, it is important to integrate the patient's desired outcomes with the health care professional's goals. The therapeutic plan is then formulated to achieve these consensus goals, which are reiterated throughout treatment. Changes can be made over time, as agreed, to accommodate both the patient and the clinician. Key aspects of the harmonization process are highlighted in *Box 1*.

Box 1. Harmonization of Treatment Goals

- Understand the patient's motivation for weight loss; meet them there.
- Explain to the patient the effects of weight on health and establish health goals of treatment (ie, complications-centric care).
- Agree on realistic consensus goals of therapy; this can boil down to degree of weight loss desired by patient and the treatment of obesity as a disease by the health care professional (adiposity-based chronic disease).
- Reinforce the consensus objectives throughout therapy.
- Emphasize that these goals can only be maintained with long-term adherence to the treatment plan. Address the need for long-term treatment early on based on obesity pathophysiology.

To promote long-term persistence on obesity medications, the therapeutic plan should produce a sufficient level of equilibrium weight loss that

Box 2. Weight-Loss Plateau

- All treatments involve an active weight-loss phase leading to a weight-loss plateau.
- This is a predictable and hardwired aspect of obesity care, a physiological necessity.
- For any given intervention, there is a wide range of individual responses for the level of the weight-loss plateau. Intensification of lifestyle therapy or a different obesity medication may be warranted to reach the weight-loss target.
- Moderate early weight loss (<5% at 3 months on the treatment dosage) could portend inadequate weight loss at 1 year and signal the need for more aggressive intervention.
- Inform patients that there will be an equilibrium to weight loss, so they know to expect it.
- Do not blame patients if the initial degree of weight loss is less than desired. It is not their fault. Assure them you are there to help them achieve the consensus goals of therapy.
- Reaching a plateau that achieves the consensus goals of therapy will predictably enhance longer-term adherence.

Box 3. Psychological Conditions Associated With Obesity That Should Be Addressed to Promote Long-Term Adherence

Identify psychological impediments

- ✓ Depression
- ✓ Anxiety
- ✓ Disordered eating
- ✓ Diminishing self-efficacy, self-esteem
- ✓ Stigma, internalized weight bias
- ✓ Work-related, family, or personal stress

Possible interventions

- ✓ Psychological screening
- ✓ Counseling
- ✓ Referral
- ✓ Cognitive behavioral therapy
- ✓ Social work consultation
- ✓ Medications
 - Antidepressant agents
 - Anxiolytics
 - Obesity medications to address cravings
 - Lisdexamfetamine

safely achieves the consensus goals of treatment. Considerations regarding the weight-loss plateau are outlined in *Box 2*.

Obesity is associated with several psychological issues and disorders listed in *Box 3*. If these issues are not addressed upfront and throughout obesity management, adherence, the effectiveness of the weight-loss intervention, and the benefits for disease outcomes can be diminished.¹⁶

Clinicians should consider social determinants of health when formulating individualized treatment plans. All factors listed in *Box 4 (following page)* can undermine short- and long-term adherence to therapy if not considered when prescribing lifestyle changes and medication.¹⁶ In particular, a patient must have access to and be able to afford the medication during both the weight-reduction and long-term management phases. Similarly, the built environment should support lifestyle therapy, including diet and physical activity prescriptions. Patient education and discussions about the consensus goals of therapy should be tailored to the patient's health literacy. Family and community support systems can be important for some patients and, if needed, can help accommodate the treatment plan. In short, it is imperative to prescribe a course of therapy that a patient can adhere to.

Many patients develop gastrointestinal adverse effects when treated with GLP-1–based medications, which can limit adherence at any point during weight reduction and long-term management. Therefore, it is important to mitigate these adverse effects, and *Box 5* offers recommendations. In phase 3 clinical trials, approximately 40% to 45% of patients developed nausea, 30% developed diarrhea, and 20% to 25% developed vomiting or constipation during therapy.^{19,20} These symptoms are generally mild to moderate and most commonly occur during dosage escalation. In clinical practice, the rate and duration of dosage escalation can be prolonged, and this is the most effective way to mitigate gastrointestinal symptoms. If these symptoms are not tolerated despite some of the interventions listed in *Box 5 (following page)*, an

alternative obesity medication could be prescribed, including a different GLP-1–based medication. The SURMOUNT 5 trial featured a 72-week head-to-head comparison of semaglutide 1.7–2.4 mg weekly vs tirzepatide 10–15 mg weekly in patients with obesity.²¹ Average weight loss was greater in the patients randomly assigned to tirzepatide. However, the percentage of patients who discontinued the medication due to gastrointestinal adverse effects was low for both drugs (2.7% for tirzepatide and 5.6% for semaglutide), and the prevalence of nausea, diarrhea, vomiting, and constipation was almost identical. It is thought that GLP-1 receptor agonists activate neurons in the area postrema and mediate gastrointestinal symptoms in many but not all patients, which requires management to ensure long-term adherence to these medications.

Despite the advent of second-generation GLP-1–based medications with unprecedented efficacy, the management of obesity as a chronic disease remains substandard. Only 50% or fewer patients remain on prescribed medications after 1 year.^{11,12} Because the pathophysiological drivers of excess adiposity persist, most patients experience weight regain and lose health benefits once medications are discontinued. Lifestyle interventions alone do not address this underlying pathophysiology, which explains why most patients are not successful with lifestyle therapy alone to maintain weight loss.

The major challenge clinicians now face is maintaining treatment adherence to sustain the weight-reduced state over the patient's lifetime. Second-generation medications have been approved only since 2021, and there is no long-term experience with these drugs. From the outset, patient management should be oriented toward effective chronic pharmacotherapy, as described in the preceding sections of this chapter. Once patients enter the phase of long-term management after weight reduction, clinicians should be prepared to creatively address the issues unique to each patient that diminish persistence with medical therapy. Some potential approaches are shown in *Box 6 (following page)*. It would be helpful to have

Box 4. Social Determinants of Health to Consider to Promote Long-Term Treatment Adherence

Social determinants

Economics

- ✓ Can't afford treatment, change in income
- ✓ Change in health insurance

Built environment

- ✓ Limited access to unprocessed food
- ✓ Limited access to physical activity

Cultural and Personal Factors

- ✓ Personal and cultural preferences for diet, activity, body image
- ✓ Support systems
- ✓ Work patterns (night shift), time management

Education

- Health literacy, numeracy

Possible interventions

- ✓ Counseling (personal and family)
- ✓ Dietician referral
- ✓ Education
- ✓ Social work referral
- ✓ Information regarding community resources

Box 5. Tips for Managing Gastrointestinal Adverse Effects of GLP-1 Receptor Agonists

- Educate patients in advance about the possibility of gastrointestinal adverse effects.
- Slowing the rate of dosage escalation is the best way to mitigate gastrointestinal adverse effects, including by de-escalating the dosage.
- Find the “maximum tolerated dosage” and determine whether consensus treatment goals are met; determine the “minimum effective dosage” that achieves health goals, since some patients are highly responsive to a submaximal dosage.
- Encourage water intake, lots of it.
- When symptoms occur, advise the patient to eat slowly, eat smaller meals, reduce fat intake, and identify and avoid problematic foods.
- Engage patients empathetically and let them know you are there to support them.
- Consider switching to a different obesity medication.
- Can use gastrointestinal medications: ondansetron and over-the-counter laxatives.
- Adjust blood pressure and diabetes medications as needed.

Box 6. Tips for Promoting Long-Term Adherence to Obesity Medical Therapy

- Ensure the patient can afford and has access to the prescribed medication.
- Try a lower dosage of the same medication used to achieve equilibrium weight loss.
- Reduce and modulate medication dose or frequency (“microdosing”) to maintain the desired level of weight loss.
- “Take a break” from medication, but enter into a contract with the patient to resume therapy if there is a specified amount of weight regain.
- Use a different medication that is less expensive, more available, or better tolerated (eg, generic liraglutide, phentermine/topiramate, naltrexone/bupropion, or future therapies such as long-acting amylin).
- Try oral GLP-1 medications for those who prefer the oral route.
- Combination therapy involving a lower dosage of GLP-1–based medication to reduce adverse effects, plus another medication to preserve efficacy.

a medication that is sufficiently effective, well-tolerated without gastrointestinal adverse effects, has demonstrated long-term safety, is eminently accessible and affordable, and can be managed within the context of an evidence-based chronic care model involving our health care systems.

While we currently lack data on the long-term use of second-generation GLP-1–based medications, help may come from several sources. First, clinical trials are warranted that address the effectiveness of strategies for long-term therapy. For example, in the ongoing SURMOUNT-MAINTAIN phase 3B trial, patients are treated open-label with tirzepatide 10 to 15 mg to achieve equilibrium weight loss at 60 weeks, followed by blinded randomization to placebo, tirzepatide 5 mg, or tirzepatide 10 to 15 mg to week 112 to determine if the lower 5 mg dose will sustain weight loss and accompanying health benefits.²² Knowledge will also come from clinicians who make the necessary adjustments to maintain long-term medication adherence, perhaps using some of the tips illustrated in *Box 6*. It will be important for clinicians to publish their experiences to identify effective practices. Finally, knowledge may come from the patients themselves. Patients are experimenting with “microdosing”; that

is, manipulating dose amount and frequency, usually using multidose pens or vials, ideally in consultation with their health care professional.^{23,24} While this is not currently recommended, anecdotally, some patients are able to find dosing strategies that curb appetite sufficiently to maintain a desired level of weight loss. The analogy is informed patients with type 1 diabetes who learn to manipulate doses of rapid-acting and basal insulin on their own to maintain glucose control over changing life conditions. Perhaps we can study strategies derived from patient practices to assess the efficacy and safety of approaches that could promote long-term medication adherence.

We can also look forward to an exciting pipeline of obesity medications in development, many of which have already demonstrated second-generation efficacy in phase 1 and 2 trials. Some medications have novel mechanisms of action and the potential to improve tolerability (eg, long-acting amylin agonists). These medications are being combined with lower dosages of GLP-1 receptor agonists to maintain efficacy while improving tolerability. We are also seeing the advent of oral GLP-1 receptor agonists, which may improve adherence among patients who prefer this route of administration. Antibody-, small interfering RNA-, and transgene-based medications have the potential to be administered less frequently (eg, every 6 months or longer), which could facilitate long-term adherence. While we have plenty of work to do, we are fortunate to be practicing in this exciting era of new drug discovery for ABCD.

Clinical Case Vignettes

Case 1

Patient Reaches Weight-Loss Plateau and Disengages From Treatment

A 58-year-old woman desires weight loss and wants to feel more energetic and be a role model for her granddaughters. She has gained weight progressively since pregnancy at age 27. She tried a low-carbohydrate diet last year but regained the weight. She has a history of hypertension treated

with losartan/hydrochlorothiazide; elevated LDL-cholesterol levels treated with atorvastatin (20 mg daily); and depression treated with duloxetine (60 mg daily). She is divorced and works as a paralegal. She has fatigue and insomnia.

On physical examination, her BMI is 38 kg/m², and blood pressure is 148/94 mm Hg. Laboratory testing documents:

Fasting glucose = 104 mg/dL (SI: 5.8 mmol/L)
 LDL cholesterol = 120 mg/dL (SI: 3.11 mmol/L)
 Triglycerides = 165 mg/dL (SI: 1.86 mmol/L)
 HDL cholesterol = 38 mg/dL (SI: 0.98 mmol/L)

Polysomnography shows an apnea-hypopnea index of 35.

The patient desires weight loss to feel better about herself, be more energetic and active, and be respected by her granddaughters. You, the health care professional, communicate the need for therapy to improve health by preventing progression from prediabetes to type 2 diabetes, lowering blood pressure, improving dyslipidemia, and ameliorating sleep apnea and its associated symptoms.

The clinical goals of therapy for this patient include: (a) preventing progression from prediabetes to type 2 diabetes, (b) lowering blood pressure, and (c) treating obstructive sleep apnea.

What is the minimum weight-loss threshold for predictable, clinically significant improvements in this patient's complications?

- A. 5%
- B. 10%
- C. 20%
- D. 30%

Answer: B) 10%

Treatment of obesity-related complications requires varying degrees of weight loss to achieve predictable clinical benefits.⁴ The Look Ahead Study in type 2 diabetes demonstrated that intensive lifestyle intervention leads to progressive decrements in blood pressure with increasing weight loss beyond 5%.²⁵ The Sleep Ahead study,²⁶

ancillary to the Look Ahead Study, and a clinical trial using phentermine/topiramate²⁷ both showed that a weight loss of 10% or more (Answer B) is required for predictable improvements in the apnea-hypopnea index in patients with sleep apnea. The data on diabetes prevention are more nuanced. In patients with prediabetes, maximal prevention of progression to diabetes in the Diabetes Prevention Project occurred with 7% to 10% weight loss,²⁸ and in a study using phentermine/topiramate, progression to overt type 2 diabetes was prevented by 80% compared with placebo after achieving approximately 10% weight loss.²⁹ Bariatric surgery can produce greater weight loss, but diabetes prevention still amounted to 80%.^{30,31} These studies could be interpreted to mean that 10% weight loss is maximal for diabetes prevention and that 20% of patients with prediabetes progress to type 2 diabetes independent of weight loss. Diabetes prevention can be achieved in approximately 90% with semaglutide 2.4 mg^{32,33} and tirzepatide 10–15 mg³⁴; however, the increase in efficacy from 80% to 90% may reflect the incretin properties of these medications. Thus, 10% weight loss is the best answer to this question.

Case 1, Continued

Initial therapy consists of a structured lifestyle intervention with dietary advice from a dietitian and a walking program for physical activity. Tirzepatide is initiated with a dosage escalation to 15 mg weekly subcutaneously. Atorvastatin is increased to 40 mg daily, and ezetimibe is added at 10 mg daily. One year into therapy, the patient has lost 10% of her body weight, which has been stable for the past 5 months despite her continued work on her meal plan and walking program. She generally feels better and interacts more with her granddaughters. Her blood pressure target has not been met. She says she is not losing more weight and wants to stop paying for the medication. She discontinued the weight-loss medication 1 month ago (ie, plateau disengagement).

Which treatment option is *not* preferable for the patient at this stage?

- A. Tell the patient she needs to work harder
- B. Suggest a “contract” where she remains off medication, continues lifestyle modifications, and weighs herself at intervals; if the weight rises 10% above the current level, she should return to the clinic and restart medication
- C. Add a non-GLP-1-based medication to her regimen (phentermine/topiramate, naltrexone/bupropion)
- D. Reinforce that the original consensus goals for treatment are largely met: “Success is staying where we are”; weight regain is likely if medication is discontinued
- E. Determine if cost is the “real issue” and suggest lower-cost treatment options

Answer: A) Tell the patient she needs to work harder

Telling the patient she needs to work harder (Answer A) could be harmful, particularly for patients with depression or high levels of internalized weight bias. As illustrated in *Figure 2*, this response could elicit psychological reactions in a patient frustrated by failing to achieve the desired weight loss, leading to self-blame and diminished self-efficacy. The preferred response is to tell the patient that this is not their fault and to be empathetic and supportive of therapeutic modifications to achieve therapeutic goals. Also,

Answer C involves combination therapy, which constitutes off-label use of these medications. While combination therapy is used in real-world practice, safety data are lacking, and health care professionals should proceed cautiously after discussing benefits and risks with the patient.

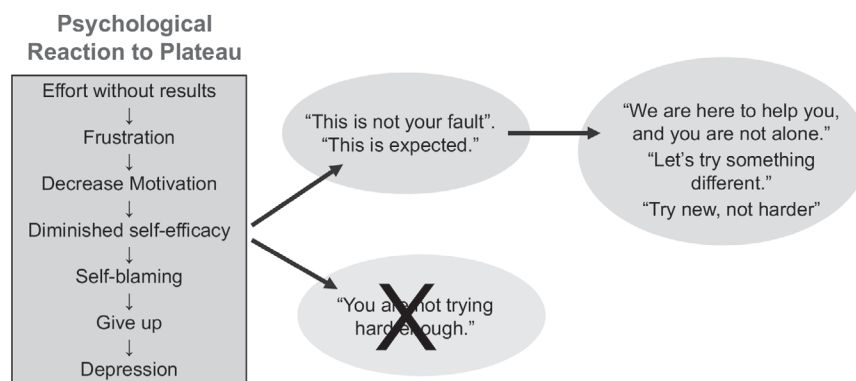
Case 2**Too Much Weight Loss**

A 34-year-old woman (BMI = 31 kg/m²) seeks weight-loss treatment. She has a history of prediabetes and hypertension, treated with hydrochlorothiazide. Semaglutide is initiated, and she reaches a dosage of 2.4 mg weekly by the fourth week. By 10 months, she has lost 60 lb (27.2 kg), down to a BMI of 21 kg/m² (32% total weight loss). She reports a profound decrease in appetite and consumes fewer than 1000 calories per day. She is taking a vitamin, but no other medications, as her blood pressure and glucose have normalized with the weight loss. She describes overall fatigue, cognitive “foginess,” muscle loss, notably in her legs, hair thinning, and oligomenorrhea (ie, “the fatigue syndrome”).

Which of the following is the best next step in this patient’s management?

- A. Instruct the patient to eat more and provide menus with nutrient-dense meals
- B. Switch to liraglutide, 3 mg daily

Figure 2. Potential Psychological Reactions When Results of Initial Therapy Fall Below Expectations and the Preferred Response From Health Care Professionals



[Color—Print (Color Gallery page CG4) or web & ePub editions]

- C. Instruct the patient to consume 2 to 3 high-protein shakes per day
- D. Decrease dosage of semaglutide from 2.4 mg to 0.5 mg weekly
- E. Switch to tirzepatide

Answer: D) Decrease dosage of semaglutide from 2.4 mg to 0.5 mg weekly

The message is that not every patient needs 20% or more weight loss, and health goals can often be achieved with 10% to 15% weight loss or with a submaximal medication dosage. Obesity is a heterogeneous disease, and some patients are highly responsive even to low doses. Some patients experience excessive, unhealthy weight loss that requires active management. This patient is experiencing profound loss of appetite, will not be able to increase caloric intake in response to this advice (Answer A), and may also have difficulty consuming the high-protein shakes (Answer C). Reducing the dosage of the current medication (Answer D) is often beneficial for slowing the rate of weight loss or allowing some weight regain, and some patients may need a temporary cessation of the medication. Nutritional assessment is important, and special caution should be exercised when treating elderly patients (sarcopenia, osteopenia, falls, and the need for clear health-related goals).

Case 3

Will Social Determinants of Health Render the Treatment Plan Ineffective?

You have been following a 58-year-old man with hypertension and chronic kidney disease (estimated glomerular filtration rate = 55 mL/min per 1.73 m²), treated with lisinopril. His BMI is 41 kg/m², but he has been reluctant to discuss his weight until today's visit. He gives you the opportunity to explain how his weight could be affecting his health and to initiate an evaluation for obesity. He has unsuccessfully tried to lose weight on his own by following various diets. His history is notable for depression treated with fluoxetine and for knee pain that makes walking difficult. He

was divorced 5 years earlier, has no children, and lost his job last month. Knee X-rays show bilateral joint space narrowing.

Your treatment plan includes a lifestyle intervention featuring a Mediterranean diet with a 500 kcal/day deficit, walks in the neighborhood as tolerated, and semaglutide with dosage escalation up to 2.4 mg weekly. At 6 months, the patient has made little progress, and weight loss totals only 1% to 2%. What went wrong? Why was the early response to therapy ineffective? On questioning, you find that he does not have access to foods compatible with a Mediterranean diet and that he cannot afford the obesity medication.

What is the preferred approach to this patient's ongoing treatment?

- A. Switch to tirzepatide
- B. Intensify lifestyle modifications without obesity medication
- C. Reinforce that his health is of paramount importance and suggest that he reorder his budget priorities
- D. Tell him to find a clinical trial
- E. Prescribe phentermine/topiramate after social work consult establishes financial feasibility

Answer: E) Prescribe phentermine/topiramate after social work consult establishes financial feasibility

The cost of second-generation obesity medications is the leading reason patients discontinue them.^{14,15} Up to one-fourth of patients do not fill their prescription, and after 1 year, fewer than 50% remain adherent.^{11,12} This should have been explored during the pretreatment phase when devising the therapeutic approach, and it would have been important to note the recent job loss. Lifestyle interventions alone are unlikely to succeed, given his history of failing multiple diet plans. An evaluation for depression may be warranted. It is important to consider social determinants of health and the psychological overlay of obesity when first developing individualized treatment plans.¹⁶

Key Learning Points

- Patient care practices during (a) the pretreatment evaluation and consensus-building on desired outcomes with the patient, (b) the weight-reduction phase, and (c) long-term management can facilitate adherence to a complications-centric therapeutic plan that optimizes health for patients living with obesity.
- To achieve optimal outcomes, clinicians should address psychological disorders, internalized

weight bias, and social determinants of health when developing an individualized care plan that supports long-term adherence to therapy.

- Health care professionals need to be flexible in response to patients' predilection to discontinue pharmacotherapy. To ensure long-term persistence with medications, clinicians can consider lower dosages or less frequent administration, alternative medications that are better tolerated or more accessible and affordable, oral medications based on patient preference, and combination therapy.

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Navigating Obesity Management in Menopause and Midlife: Endocrine Mechanisms and Clinical Management

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Diagnose and differentiate premenopause, perimenopause, and menopause in midlife women presenting with weight gain or central adiposity by using clinical features and appropriate hormonal evaluation.
- Differentiate the causes of obesity in menopausal women, including menopause-related physiologic changes in body composition, endocrine disorders, lifestyle contributors, and central fat redistribution, using waist-based metrics alongside BMI.
- Explain the metabolic effects of menopausal hormone therapy (MHT) and emerging alternatives, including their influence on fat distribution and insulin sensitivity, and their potential integration with lifestyle and pharmacologic treatments. Furthermore,

recognize nonhormonal modifiers of metabolic risk during menopause, including diet quality, energy expenditure, sleep disruption, and adipokine involvement (eg, leptin).

Significance of the Clinical Problem

Introduction

Menopause is defined as the permanent cessation of ovarian function and menstrual cycles due to follicular depletion and is accompanied by profound hormonal changes, particularly a decline in circulating estrogen levels.¹ Over the past century, demographic changes have dramatically altered the clinical significance of menopause, as approximately 95% of women now reach menopause, and many spend more than 3 decades in the postmenopausal state. Consequently, menopause-related metabolic disorders have become a major public health

concern, with obesity playing a central role.² Obesity is increasingly recognized as a chronic, relapsing disease characterized by complex interactions among genetic, epigenetic, biological, behavioral, and environmental factors, with a disproportionate rise among midlife women.³ In this population, weight gain is frequently accompanied by increased visceral adiposity, a hormonally mediated shift that emerges during the menopausal transition and is strongly associated with cardiometabolic risk.^{4,5} Epidemiological data consistently demonstrate that obesity prevalence increases with advancing age, especially among women transitioning through midlife.⁶ The STRAW+10 (Stages of Reproductive Aging Workshop) classification provides a standardized framework for defining the stages of reproductive aging, including the reproductive stage, menopausal transition, and post menopause, based on menstrual patterns and hormonal changes, enabling more consistent clinical characterization and risk assessment.¹ Menopause should therefore be viewed not only as a reproductive milestone but also as a major metabolic transition affecting energy balance, adipose tissue distribution, and cardiometabolic risk.⁷ Despite these well-recognized changes, menopause-associated alterations in body composition and metabolic risk remain underrecognized in clinical practice. Importantly, beyond changes in total body weight, midlife women often exhibit declines in insulin sensitivity, adverse lipid profiles, and increased inflammatory markers that precede the development of overt metabolic disease, alongside a range of menopausal symptoms affecting quality of life.⁸⁻¹⁰

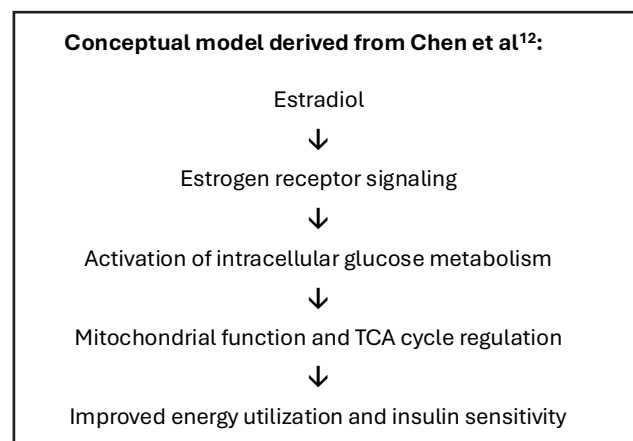
Background

Estrogen Depletion

Although lifestyle factors, such as diet, physical activity, and sleep, remain important, accumulating evidence suggests that menopause is accompanied by intrinsic metabolic adaptations related to estrogen decline. These changes include reductions in resting and total energy expenditure that occur independently of chronological aging, alterations in adipose tissue biology, and changes in central appetite regulation that together favor

positive energy balance.^{7,11} Declining estrogen levels are associated with reductions in basal metabolic rate, increased central adiposity, and impaired cardiorespiratory fitness, which may increase perceived exertion and reduce exercise tolerance. Estrogens play a central role in metabolic homeostasis by regulating appetite, energy expenditure, glucose metabolism, and lipid metabolism.¹² Their decline disrupts adipokine signaling, reducing beneficial mediators such as adiponectin while altering leptin sensitivity, thereby promoting a proinflammatory and insulin-resistant metabolic state.^{8,13} At the cellular level, estradiol supports mitochondrial energy production and intracellular glucose metabolism, influencing key metabolic pathways, including glycolysis and the tricarboxylic acid (TCA) cycle (*Figure 1*). Experimental studies further demonstrate that estrogen replacement in ovariectomized animals prevents weight gain and protects against insulin resistance.¹⁴ Nevertheless, menopause is not inevitably associated with absolute weight gain; rather, it is characterized by preferential redistribution of adiposity toward visceral depots, even in the absence of significant changes in BMI. This period represents a critical window for prevention and intervention, yet menopause-specific metabolic drivers are frequently overlooked or misattributed to chronological aging alone.²

Figure 1. Estradiol Regulation of Cellular Energy Metabolism



Derived from Chen JQ et al. *Biochim Biophys Acta*, 2009; 1793(7): 1128-1143. © Elsevier B.V.

Clinical Impact

One of the most significant metabolic changes during menopause is the shift in body fat distribution from a gynoid to an android pattern characterized by increased visceral adipose tissue accumulation and reduced lean body mass.⁷ Visceral adiposity is strongly associated with insulin resistance, dyslipidemia, and chronic low-grade inflammation, representing a major driver of cardiometabolic risk in postmenopausal women. Thus, waist circumference, waist-to-hip ratio, and waist-to-height ratio are better predictors than BMI alone (European Association for the Study of Obesity [EASO] guidelines) (*Table 1*).^{15,16} Importantly, this redistribution can occur even without major changes in body weight. Although BMI remains the most widely used measure for obesity classification, it does not adequately capture fat distribution or visceral adiposity, both of which are more closely associated with cardiometabolic risk. Accordingly, measures of central adiposity, including waist circumference, waist-to-hip ratio, waist-to-height ratio, and emerging indices such as the lipid accumulation product (LAP) and A Body Shape Index (ABSI), provide more clinically relevant assessments of cardiometabolic risk (EASO guidelines).^{3,16} Although obesity is conventionally defined by a BMI of 30 kg/m² or higher, waist circumference (>35 in [>88 cm] in women) and waist-to-height ratio (≥ 0.5) more accurately reflect central adiposity and cardiometabolic risk.¹⁵ Recognition of menopausal status and fat distribution patterns is therefore essential for early risk stratification

and for guiding targeted hormonal, lifestyle, and pharmacologic interventions. Recent approaches also emphasize obesity phenotyping, recognizing that individuals with similar BMI values may exhibit markedly different metabolic risk profiles depending on fat distribution and metabolic health.³ Longitudinal cohort studies, including the Study of Women's Health Across the Nation (SWAN), further demonstrate that the menopausal transition is associated with progressive increases in central adiposity and adverse metabolic changes, even when overall body weight remains relatively stable.^{17,18} Surgical menopause is further associated with an increased risk of severe obesity, particularly among women undergoing bilateral oophorectomy.⁶

Practice Gaps

- Identifying increased visceral fat as an early clinical sign of estrogen deficiency during the menopausal transition.
- Recognizing the beneficial role of MHT (focusing on the addition of estrogens) in reducing visceral fat, and considering it only when indicated according to the corresponding guidelines. Of note, a decrease in visceral fat or body weight does not, per se, constitute an indication for MHT.
- Recognizing that MHT enhances the beneficial effects of exercise (specifically resistance exercise) in menopausal women with obesity.
- Considering the therapeutic conundrum in women with obesity (particularly when BMI exceeds 30 kg/m² or in women with class 3 obesity), as MHT may be beneficial in reducing visceral adipose tissue, yet it could contribute to thromboembolic events.
- Recognizing other endocrine changes during this period of a woman's life that affect adipose tissue metabolism and body weight.

Table 1. Anthropometric Indicators of Visceral Adiposity

Measurement	Clinical significance
BMI	General measure of obesity but limited in detecting visceral fat
Waist circumference	Indicator of abdominal obesity
Waist-to-hip ratio	Reflects central fat distribution
A Body Shape Index	Predicts cardiometabolic risk
Lipid accumulation product	Reflects visceral fat and lipid metabolism

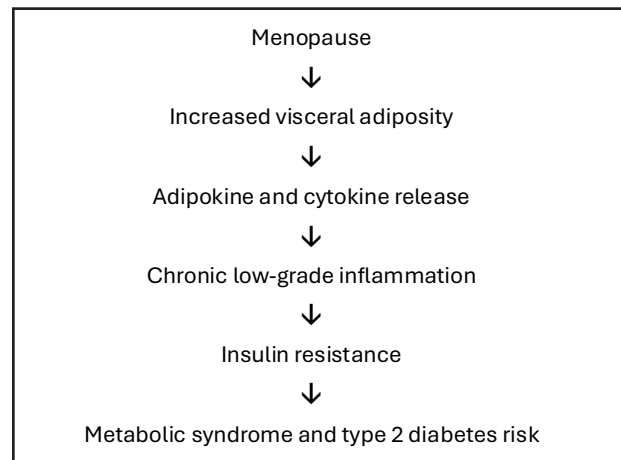
Discussion

Menopause is associated with major metabolic changes that increase the risk of obesity and cardiometabolic disease, mainly due to declining estrogen levels, which influence body composition, fat distribution, and energy homeostasis.² Experimental and clinical models show that gradual estrogen deficiency promotes insulin resistance, increases visceral adiposity, and disrupts adipokine signaling, including leptin, adiponectin, and kisspeptin pathways.^{12,19} Observational data further suggest that earlier menopause is associated with a higher risk of metabolic disorders, including type 2 diabetes (T2D).²⁰⁻²² The resulting increase in visceral adiposity is pathophysiologically active. Estrogen deficiency promotes lipolysis within adipose tissue, increasing circulating free fatty acids that impair insulin signaling in hepatic and skeletal muscles. Concurrently, altered adipokine profiles (reduced adiponectin and impaired leptin signaling) create a proinflammatory, insulin-resistant state that may appear as impaired glucose tolerance or fasting hyperinsulinemia, thereby increasing the risk of cardiovascular events.¹³ Notably, these metabolic shifts can occur independently of absolute weight gain. Menopause-related metabolic alterations reflect the interaction between hormonal decline and neuroendocrine pathways that regulate energy balance. Multiple endocrine pathways regulating metabolic health (including insulin, leptin, cortisol, and thyroid hormones) may be dysregulated in midlife women with estrogen deficiency.

Insulin

Menopause is associated with increased insulin resistance and hyperinsulinemia. Visceral adipose tissue contributes to this process by releasing inflammatory mediators, such as TNF, IL-6, and IL-1, as well as adipokines (*Figure 2*). Vasomotor symptoms, including hot flashes and night sweats, have also been associated with increased insulin resistance and cardiometabolic risk, suggesting an underlying link between neurovascular regulation and metabolic dysfunction.^{2,8,23}

Figure 2. Mechanisms Linking Visceral Fat and Insulin Resistance



In addition, visceral adiposity and insulin resistance during menopause are closely linked to the development of metabolic dysfunction-associated steatotic liver disease (MASLD). Postmenopausal women exhibit increased hepatic fat accumulation, largely driven by central adiposity, altered lipid metabolism, and chronic low-grade inflammation.^{24,25} MASLD is increasingly recognized as part of the broader cardiometabolic risk profile associated with menopause. The close interaction between visceral adiposity and glucose dysregulation has been described as “diabesity,” highlighting the strong link between obesity, insulin resistance, and the development of T2D.²⁶

Leptin

Leptin regulates appetite and energy balance through hypothalamic signaling pathways. In postmenopausal women, leptin resistance may develop due to altered signaling mechanisms. Experimental and clinical evidence suggests that hypothalamic inflammation may contribute to this process by disrupting leptin signaling pathways involved in appetite regulation and energy homeostasis. Dysregulation of leptin and associated neuroendocrine pathways may contribute to obesity (*Table 2, following page*).^{13,19,27}

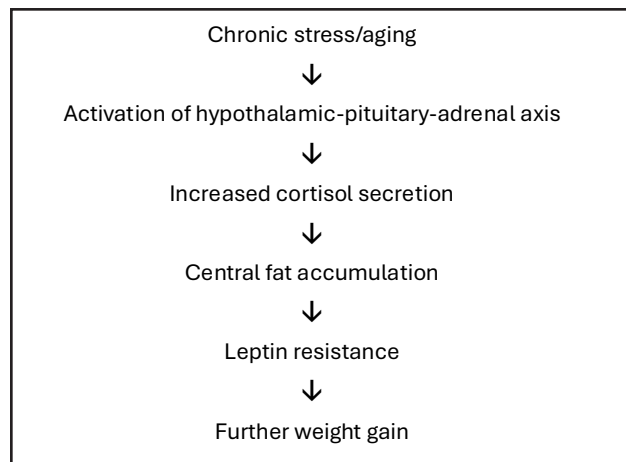
Table 2. Neuroendocrine Regulators of Appetite in Menopause

Hormone	Function	Menopause-related change
Leptin	Satiety hormone	Possible leptin resistance
Kisspeptin	Regulates reproductive and metabolic signaling	Dysregulation may affect appetite
Ghrelin	Stimulates hunger	May interact with energy balance
Insulin	Regulates glucose metabolism	Increased resistance

Cortisol and the Stress Axis (Figure 3)

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in metabolic regulation. Aging and chronic stress may increase cortisol secretion, which promotes abdominal fat deposition.^{28,29}

Figure 3. Interaction Between Stress, Cortisol, and Obesity



Thyroid Hormones

Thyroid dysfunction can contribute to metabolic changes during menopause. Climacteric women have been observed to use thyroid medication more often than premenopausal women, although the prevalence of overt thyroid disease may not differ significantly.³⁰

In addition to biological factors, lifestyle behaviors and psychosocial influences play important roles in the development of obesity.

Management

Effective management of obesity during menopause requires a holistic strategy that includes dietary interventions, regular physical activity, behavioral therapy, and pharmacological treatment when appropriate. Even modest weight reduction of 5% to 10% can significantly improve metabolic parameters and menopausal symptoms. Contemporary obesity management guidelines recommend a stepwise therapeutic approach that includes lifestyle modification, pharmacotherapy when indicated, and metabolic or bariatric surgery for severe obesity.

Lifestyle Modification

Lifestyle modification remains the foundation of obesity management for women with obesity during menopause. Even modest weight loss of 5% to 10% can significantly improve metabolic abnormalities associated with insulin resistance. Reported benefits include improved glycemic control, reduced cardiovascular risk factors, and even improvements in vasomotor symptoms such as hot flashes.^{31,32}

Nutritional Interventions

The Mediterranean diet has been associated with multiple metabolic benefits and stands out for several positive aspects (*Table 3*).³³ It emphasizes fruits, vegetables, whole grains, olive oil, fish, and moderate dairy consumption.

Table 3. Effects of the Mediterranean Diet in Menopausal Women

Outcome	Observed effect
Body weight	Reduction
Blood pressure	Reduction in systolic and diastolic blood pressure
LDL cholesterol	Reduction
Triglycerides	Reduction
Omega-6 to omega-3 ratio	Improvement in fatty acid balance

Physical Activity

Exercise is essential for maintaining metabolic health in menopausal women (*Table 4*).³¹ During the menopausal transition, women often engage in less physical activity, reflecting both advancing age and menopause-related metabolic and biological changes.² Declining estrogen levels are associated with reductions in basal metabolic rate, increased central adiposity, and impaired cardiorespiratory fitness, which increase perceived exertion and reduce exercise tolerance.¹¹ Sleep disturbance and stress-related neuroendocrine alterations (such as dysregulation of leptin and HPA axis activity) may further deplete available energy and reduce habitual physical activity.^{13,28} Together, these factors reduce exercise engagement beyond the effects of chronological aging alone.

Current recommendations include:

- At least 150 minutes of moderate physical activity per week
- A combination of aerobic and resistance training^{34,35}

Table 4. Benefits of Exercise in Menopausal Women

Exercise type	Major benefits
Aerobic exercise	Reduces visceral fat
Resistance training	Preserves muscle mass
Combined programs	Improves metabolic health

Behavioral Interventions

Psychological factors influence weight gain during menopause. Cognitive behavioral therapy may support lifestyle interventions by improving adherence and addressing emotional barriers.³⁶

Table 5. Pharmacologic Options for Obesity in Menopause

Drug class	Examples	Mechanism
Insulin sensitizers	Metformin, pioglitazone	Improve insulin sensitivity
Lipase inhibitors	Orlistat	Reduce fat absorption
GLP-1 and GIP receptor agonists	Tirzepatide, semaglutide, liraglutide, etc	Reduce appetite, delay gastric emptying, improve glycemic control
Hormone therapy	Estrogen therapy	May improve body fat distribution

Menopausal Hormone Therapy

MHT may be considered for symptomatic women; however, obesity influences treatment decisions. Women with a BMI greater than 30 kg/m² may be at increased risk of adverse effects from certain hormonal therapies, whereas transdermal estradiol may be a safer option in some cases because of its lower thrombotic risk.³⁷

Therefore, clinical decision-making should be individualized, balancing symptom relief with cardiometabolic risk. In premenopausal women, treatment with cyclical micronized progesterone or the levonorgestrel-releasing intrauterine system may also be considered. It should be noted that hormone therapy does not consistently produce significant weight loss, although it may reduce central fat accumulation.^{38,39}

Pharmacologic Treatment

Pharmacologic therapy is recommended when lifestyle interventions fail (*Table 5*). Metabolic or bariatric surgery may be considered for patients with severe obesity or obesity-related complications when lifestyle and pharmacologic interventions are insufficient.^{34,40}

Prevention and Clinical Implications

Preventing obesity during menopause requires a life-course approach. Health care professionals should promote healthy dietary habits, physical activity, and weight maintenance beginning early in life. Addressing environmental factors that contribute to obesity, such as sedentary lifestyles and high-calorie diets, is also critical.³

Conclusion

Menopause represents a period of profound metabolic change characterized by increased visceral adiposity and elevated cardiometabolic risk. Estrogen deficiency interacts with multiple endocrine pathways, including insulin, leptin, cortisol, and thyroid hormones, to influence energy balance and fat distribution. Importantly, these metabolic changes may occur even in the absence of significant increases in total body weight, highlighting the limitations of BMI as the sole indicator of metabolic risk in midlife women. Management requires a comprehensive approach that integrates lifestyle modifications, behavioral strategies, and, when necessary, pharmacologic interventions. Even modest weight loss can significantly improve metabolic health and quality of life for menopausal women. Further research is needed to better understand the complex endocrine mechanisms underlying obesity during menopause and to identify optimal prevention and treatment strategies.

Clinical Case Vignettes

Case 1

A 54-year-old woman presents with the following concerns:

- Amenorrhea for 9 months
- Weight gain of approximately 18 lb (8 kg) over 2 years
- Central fat accumulation in the abdomen
- Frequent hot flashes and night sweats
- Fatigue and depressed mood during dieting
- Vaginal and generalized dryness

Her BMI is 31.8 kg/m², and waist circumference is 37 in (93 cm). She has had controlled hypertension since age 51 years. She has newly diagnosed dyslipidemia (elevated total and LDL cholesterol).

Laboratory test results:

Fasting glucose = 118 mg/dL (SI: 6.55 mmol/L)
Elevated insulin with insulin resistance (HOMA-IR = 6.7)

To establish management options, which of the following clinical observations would be your priority target?

- Fasting glucose
- Elevated insulin with insulin resistance
- Waist circumference and BMI
- Waist circumference, BMI, and menopausal symptoms
- Dyslipidemia

Answer: D) Waist circumference, BMI, and menopausal symptoms

The correct answer is waist circumference, BMI, and menopausal symptoms (Answer D) because it addresses the management of the deleterious effects of visceral fat, total body fat, and estrogen deficiency.^{2,7,8}

The second-best option is waist circumference and BMI (Answer C) because it addresses the harmful effects of both visceral and total body fat. Central obesity is strongly associated with insulin resistance and cardiometabolic risk, explaining impaired glucose metabolism and dyslipidemia.

Treating only elevated glycemia (Answer A) (lifestyle modifications, metformin) would neglect the menopause-associated etiology of metabolic derangement.

Targeting only adipose tissue-associated insulin resistance (Answer B), would neglect menopause-associated insulin resistance (see Women's Health Initiative 2001).

Dyslipidemia (Answer E) targets only 1 factor of the metabolic derangement.

Case 2

A 49-year-old late perimenopausal woman presents with the following concerns:

- “My periods have become very irregular during the last year. I sometimes skip 2 or 3 months. I have gained around 13 lb (6 kg) even though my eating habits have not changed. My clothes feel tight around my waist, and I feel constantly bloated. I am worried because my mother developed diabetes in her fifties. Could this be related to menopause?”
- Sleep disturbance, difficulties in short-term memory, and fatigue
- Central weight gain

Her medical history includes a family history of T2D. She leads a sedentary lifestyle. Clinical evaluation reveals a BMI of 29.4 kg/m² and a waist circumference of 36 in (92 cm).

Laboratory test results:

Fasting glucose = 110 mg/dL (SI: 6.1 mmol/L)
 Fasting insulin = 18 μ IU/mL (SI: 125 pmol/L)
 HOMA-IR = 4.9
 Total cholesterol = 210 mg/dL (SI: 5.44 mmol/L)
 HDL cholesterol = 50 mg/dL (SI: 1.30 mmol/L)
 LDL cholesterol = 138 mg/dL (SI: 3.57 mmol/L)
 Triglycerides = 160 mg/dL (SI: 1.81 mmol/L)

Case 2, Question 1

To establish management options, which of the following clinical observations would be your priority target?

- Fasting glucose
- Bloating and menstrual irregularity
- Waist circumference and BMI
- Waist circumference, BMI, bloating, and menstrual irregularity
- Dyslipidemia
- Sleep disturbance

Answer: D) Waist circumference, BMI, bloating, and menstrual irregularity

The correct option is waist circumference, BMI, bloating, and menstrual irregularity (Answer D) because it addresses both the etiology of premenopause-associated symptoms (menstrual

irregularity, sleep disturbance, difficulties with short-term memory, and fatigue) and the etiology of weight gain during this period of a woman's life.^{2,5,23}

The second-best option is waist circumference and BMI (Answer C) because it addresses the deleterious effects of visceral and total body fat. During the menopausal transition, hormonal changes—particularly declining estrogen levels—promote central fat redistribution and increased visceral adiposity, even without significant weight gain. Obesity and increased BMI are also linked to more intense menopausal symptoms, including vasomotor disturbances and physical symptoms such as fatigue and weight gain.

Treating only elevated glycemia (Answer A) (lifestyle modifications, metformin) neglects the menopause-associated etiology of metabolic derangement and omits treatment of menstrual irregularity.

Bloating and menstrual irregularity (Answer B) includes only attention to premenopausal symptoms.

Dyslipidemia (Answer E) targets only 1 factor of the metabolic derangement.

Sleep disturbance (Answer F) does not represent a holistic approach to perimenopause-related symptoms and weight gain.

Case 2, Question 2

Which of the following would be the best treatment approach?

- Exercise and nutrition advice (weight reduction)
- Micronized progesterone or levonorgestrel-releasing intrauterine system
- Physical activity
- Micronized progesterone or levonorgestrel-releasing intrauterine system, physical activity, and nutrition advice (weight reduction)
- Physical activity, nutrition advice (weight reduction), and sleeping medication

Answer: D) Micronized progesterone or levonorgestrel-releasing intrauterine system, physical activity, and nutrition advice (weight reduction)

Micronized progesterone or a levonorgestrel-releasing intrauterine device, physical activity, and nutrition advice (weight reduction) (Answer D) is correct because this approach targets both the etiology of premenopause-associated symptoms and the etiology of weight gain during this period of a woman's life.^{32,38}

Exercise and nutrition advice for weight reduction (Answer A) does not address premenopausal symptoms.

Micronized progesterone or a levonorgestrel-releasing intrauterine device (Answer B) treats only premenopausal symptoms.

Physical activity (Answer C) is very restrictive and has not been shown to accelerate weight loss.

Treating sleep disturbance of premenopause with sleeping pills (Answer E) represents a symptomatic rather than etiologic approach.

Case 2, Question 3

And then what?

Case 3

A 58-year-old woman who has been postmenopausal for 4 years presents with the following concerns:

- "I went through menopause about 4 years ago, but the hot flashes never stopped. In fact, they seem worse now. I also feel joint pain and dryness. Over the last decade, I've gained about 26 lb (12 kg) and it seems impossible to lose. I'm worried because my blood pressure has increased, and my doctor told me my cholesterol is high."
- Severe vasomotor symptoms (frequent hot flashes)
- Joint and muscle pain
- Vaginal dryness
- Fatigue

Her medical history includes hypertension (treated) and dyslipidemia. She is a former cigarette smoker. Clinical evaluation reveals a BMI

of 33.1 kg/m² and a waist circumference of 38 in (96 cm).

Laboratory test results:

Fasting glucose = 116 mg/dL (SI: 6.4 mmol/L)
 Fasting insulin = 25 µIU/mL (SI: 173.6 pmol/L)
 HOMA-IR = 7.1
 Total cholesterol = 240 mg/dL (SI: 6.22 mmol/L)
 HDL cholesterol = 45 mg/dL (SI: 1.17 mmol/L)
 LDL cholesterol = 160 mg/dL (SI: 4.14 mmol/L)
 Triglycerides = 170 mg/dL (SI: 1.92 mmol/L)

Which of the following would be the best treatment approach?

- Physical activity and nutrition advice (weight reduction)
- Micronized progesterone or levonorgestrel-releasing intrauterine system
- Transdermal MHT with micronized progesterone or progestogen
- Transdermal MHT with micronized progesterone or progestogen, physical activity, and nutrition advice (weight reduction)
- Physical activity, nutrition advice (weight reduction), optimization of cardiometabolic risk factors, and transdermal MHT with micronized progesterone or progestogen

Answer: E) Physical activity, nutrition advice (weight reduction), optimization of cardiometabolic risk factors, and transdermal MHT with micronized progesterone or progestogen

Physical activity and nutrition advice (Answer A) does not treat menopausal symptoms. Notably, weight loss and metabolic control may improve both cardiovascular risk and menopausal symptoms.

Micronized progesterone or a levonorgestrel-releasing intrauterine device (Answer B) is not applicable in menopause.

Transdermal MHT with micronized progesterone or progestogen (Answer C) is appropriate for menopausal symptoms. However, in this case, increased BMI warrants caution. Obesity is associated with more severe menopausal

symptoms, particularly vasomotor symptoms such as hot flashes and sweating. Adipose tissue may contribute to thermoregulatory instability and hormonal imbalance, potentially increasing symptom intensity in women with obesity.

Transdermal MHT with micronized progesterone or progestogen, physical activity, and nutrition advice (weight reduction) (Answer D) is a more comprehensive approach that addresses the management of obesity (obesity in postmenopausal women is strongly linked to insulin resistance and metabolic syndrome, driven by adipocyte dysfunction and altered adipokine secretion) and menopausal symptoms. However, the correct choice is Answer E if applied in the presented order, with caution regarding MHT administration in this woman with increased BMI.^{8,31,32,37}

Key Learning Points

- Premenopause and menopause are associated with an increase in body weight, particularly with visceral fat accumulation.
- During the menopausal transition, women often exhibit reduced physical activity and energy expenditure.
- Endocrinologists should recognize weight gain and central fat redistribution as part of premenopausal and menopausal syndromes.
- Although indications for prescribing MHT do not include body weight changes, increased body weight and redistribution of body fat toward visceral depots may be considered adjunctive factors when evaluating its potential use.
- Endocrinologists should familiarize themselves with the prescription of exercise.

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Dietary Patterns and Eating Strategies in Obesity Care: Timing, Composition, and Personalized Approaches

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify the role of macronutrients and the amounts required for benefit.
 - Illustrate the value of dietary patterns and chrononutrition.
 - Review pragmatic aspects of implementing dietary patterns and eating strategies.
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Significance of the Clinical Problem

Effective obesity care requires more than simple calorie counting; it involves understanding the complex interplay of what we eat, when we eat, and how individual factors influence dietary success. Dietary patterns and eating strategies offer structured approaches to support weight management and metabolic health by emphasizing nutrient composition, meal timing, and overall eating behaviors. From well-studied patterns such as the Mediterranean and DASH diets to time-based strategies such as intermittent fasting and time-restricted eating, evidence suggests that both the quality and timing of food intake can significantly affect weight, cardiometabolic risk, and long-term adherence. Personalization,

which considers cultural background, preferences, lifestyle, and readiness for change, is essential to optimize outcomes and ensure that interventions are sustainable, practical, and free from stigma. This chapter explores the evidence, mechanisms, and clinical applications of these dietary approaches in obesity care.

Practice Gaps

- Many physicians have limited training in comparative evidence regarding how different dietary patterns, meal timing, and macronutrient composition independently affect metabolic outcomes beyond weight loss. This knowledge gap can lead to nonspecific or outdated dietary advice, reducing patient engagement and limiting improvements in weight management, glycemic control, cardiometabolic risk, and long-term adherence.
- Physicians often lack the practical skills to individualize dietary recommendations and safely implement strategies, such as time-restricted eating or low-carbohydrate diets, resulting in missed opportunities for sustainable metabolic improvement.

Discussion

The influence of diet on health and wellness has been recognized since antiquity, with some of the earliest documented evidence dating to Egyptian medical texts from approximately 2000 to 1500 BCE.¹ Sthaulya, or obesity as a disease, and dietary management thereof, was recognized in Ayurvedic medicine in ancient India dating back to 1500 BCE.² Hippocratic Corpus, a foundational Greek text in medical writings, emphasizes the harm of excess, as well as a deficient state. Some modern concepts of meal timing and an individualized approach were central to the dietary principles outlined in those ancient texts.³ Since these early influences, the role of diet in weight management has continued to evolve within modern medicine. The early era of modern medicine emphasized calorie restriction. Although that remains a germane principle in weight management, individual macronutrient manipulation gained the most traction, followed by eating patterns, including the role of timing of nutrient ingestion, and, later, more individualized approaches. The following sections examine these dietary patterns and eating strategies, along with supporting evidence.

Role of Macronutrient Quantity and Composition

There are many challenges in studying the role of macronutrients, as altering the level of one macronutrient affects the proportions of the others, making it difficult to assess the effect of true exposure. For obvious reasons, blinding is not possible. There is also no standardized definition for various macronutrient components.

Low-carbohydrate diets are widely popular and have been extensively studied. In general, 130 g of carbohydrate per day is recommended for adults.⁴ The body can generate its own energy through glycogenolysis, gluconeogenesis, and ketogenesis, thereby permitting consideration of low-carbohydrate dietary approaches. Diets that restrict carbohydrate intake to less than 10% of total daily energy intake, or to 20 to 50 g per day, are considered very-low-carbohydrate diets.^{5,6} This

degree of carbohydrate restriction, usually in the presence of high fat intake, can promote ketonuria. Protein intake may influence this, as some amino acids can serve as substrates for gluconeogenesis and impair ketone formation by stimulating insulin secretion.⁵ Although the definition of low- or moderately low-carbohydrate diets varies in the literature, diets that incorporate less than 40% to 45% of total energy intake as carbohydrates can be classified as low-carbohydrate.⁶

Low- and very-low-carbohydrate diets have been shown to produce modest weight loss, with mean weight differences ranging from −0.48 to −2.17 kg, as indicated by several meta-analyses in the setting of overweight/obesity.⁵ The effectiveness is most notable in the short term, within 3 to 6 months, but is less sustainable over time, compared with other diets.⁷ The benefit appears greater when caloric intake is restricted, potentially mediated by increased satiety and reduced hunger, effects that may be more pronounced with very-low-carbohydrate diets, likely driven by ketosis.⁸ Energy expenditure is also higher with low- and very-low-carbohydrate diets, with a linear trend of 52 kcal/d higher total energy expenditure per 10% reduction in carbohydrate contribution to total energy intake.⁹ The exact mechanism that contributes to this phenomenon remains unclear. Although this combination of reduced hunger sensation and increased energy expenditure can provide a significant advantage for very-low-carbohydrate/ketogenic diets, sustainability is a limiting factor for long-term maintenance.⁵

Low-carbohydrate diets consistently lower triglyceride levels, with the greatest reductions observed with very-low-carbohydrate diets.¹⁰ HDL cholesterol may increase modestly by 3 to 4 mg/dL (0.08–0.10 mmol/L) on low-carbohydrate diets, with greater increases in individual trials with very-low-carbohydrate diets.¹¹ A small, temporary increase in LDL cholesterol, around 2 to 4 mg/dL (0.05–0.10 mmol/L), is often seen during the first 3 to 6 months, followed by a return to baseline levels in many individuals.¹² Significant interindividual variability is noted in this response, which may be driven by saturated fat content and likely by

genetic factors.⁵ Limiting saturated fat intake may help attenuate the increase in LDL cholesterol observed with low-carbohydrate diets and may reduce potential long-term cardiometabolic risk.¹³ Some studies have found that plant-based, low-carbohydrate diets are associated with a lower risk of all-cause mortality compared with animal-based carbohydrate replacements.¹⁴ Reassessment of the lipid panel 3 to 6 months after adopting a dietary change can assess an individual's response.

Diets with less than 41% of total energy intake from carbohydrates lead to greater losses of fat mass and fat-free mass, with a magnitude of 1.74 kg. This loss of fat-free mass is mitigated by increasing protein intake.¹⁵ The National Lipid Association class IIA recommendation endorses protein intake of 1 to 1.5 g/kg per day in the context of low-carbohydrate diets to prevent loss of lean body mass.⁵

Because fats and carbohydrates account for most macronutrient intake, reductions in carbohydrate consumption are often accompanied by higher fat intake, making it difficult to isolate their independent effects. Low-fat diets may produce slightly less weight loss at 3 to 6 months than low-carbohydrate diets, but overall, there is no significant difference in weight loss at 12 months.¹⁶ The triglyceride-lowering effect of low-fat diets is more modest because of their high-carbohydrate content, with a possible risk of worsening in some individuals. Low-fat diets have minimal effects on HDL cholesterol but are associated with modest reductions in LDL cholesterol, in contrast to the LDL-cholesterol increase observed with low-carbohydrate, high-fat diets.^{16,17}

High-protein diets typically provide 1.2 to 1.6 g of protein per kg of body weight per day and account for 25% to 30% of total caloric intake.¹⁸ Higher-protein diets offer advantages over standard-protein, energy-restricted diets, including greater weight loss and better preservation of fat-free mass.¹⁹ Greater perceived fullness and enhanced satiety hormone responses have been observed after higher-protein meals, along with a favorable effect on resting energy expenditure.^{18,19} Protein intake should be limited

in the setting of kidney and/or liver impairment. There has been significant interest in metabolic and anthropometric outcomes associated with animal vs plant protein sources. In the short term, the protein source does not appear to significantly affect weight loss, satiety, or lean mass loss.²⁰ Similar weight loss is observed with high-protein diets, with 35% of total caloric intake as protein, 75% of protein from either plant or animal sources, with similar improvements in body composition, including visceral fat.²¹ No significant changes in glucose metrics, lipid profile, metabolic or inflammatory markers are noted. Large cohort studies have found that plant-based protein intake is associated with reduced mortality. Although animal protein was associated with higher cardiovascular mortality, plant protein was associated with lower all-cause and cardiovascular mortality in the Nurses' Health Study and Health Professionals Follow-Up Study. Replacing 3% of total energy from unprocessed red meat or eggs with plant protein was associated with lower all-cause mortality, with hazard ratios of 0.88 and 0.81, respectively. The effect was greater if processed red meat was replaced by plant protein, with a hazard ratio of 0.66.²² The totality of metabolic mechanisms contributing to these outcomes is yet to be completely unraveled.

Dietary Patterns and Chrononutrition

A dietary pattern is defined as the totality of foods and beverages consumed, with emphasis on overall nutritional density rather than on individual macronutrients or food groups. The Mediterranean-style diet is among the most extensively studied dietary patterns in weight management, emphasizing dark green vegetables, fruits, and nuts; moderate to high intake of fish and seafood; low intake of red meat and dairy fat; and the use of extra-virgin olive oil as the main source of dietary fat.²³ The landmark PREDIMED multicenter trial from Spain demonstrated that, among individuals at high cardiovascular risk, the Mediterranean diet reduced the incidence of

the composite primary endpoint of myocardial infarction, stroke, or cardiovascular death compared with a low-fat diet.²⁴ In analyses from the Nurses' Health Study examining individual components of the Mediterranean-style eating pattern, higher intakes of fruits, nuts, and whole grains were associated with the most favorable effects on adiponectin levels.²⁵ However, the Mediterranean diet represents a holistic way of eating rather than the sum of its individual components. In PREDIMED, an ad libitum Mediterranean diet was associated with a 0.43 kg weight loss and a -0.55 cm decrease in waist circumference. Greater weight loss is observed with an energy-restricted Mediterranean diet, particularly when combined with physical activity, as noted in the PREDIMED-Plus trial.²⁶ A study evaluating adherence to the Mediterranean diet found 0.04 kg less weight gain over 5 years for each 1-unit increase in Mediterranean diet score, a 9-component scoring system that quantifies adherence to the traditional Mediterranean dietary pattern.^{27,28}

Another dietary pattern that deserves special mention is the DASH (Dietary Approaches to Stop Hypertension) diet, which has demonstrated benefits for weight and metabolic management. The DASH diet, a dietary pattern rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat, was initially studied and shown to be beneficial for blood pressure control.²⁹ This dietary pattern has shown benefits, with weight loss averaging 1.42 kg and a mean decrease in waist circumference of 1.05 cm, with greater benefits observed with the low-calorie DASH diet.³⁰

A comparison of 14 dietary patterns categorized as low-carbohydrate, low-fat, or moderate-macronutrient (including the Mediterranean and DASH diets) showed that all diets were effective for weight reduction. Compared with a typical diet, only the Mediterranean diet produced a significant reduction in LDL cholesterol. By 12 months, the benefits for weight and cardiovascular risk factors observed with other popular diets had diminished, whereas those associated with the Mediterranean diet were largely sustained.³¹ In

individuals with type 2 diabetes, a network analysis of 73 randomized controlled trials of 8 different dietary patterns showed the largest reduction in weight at 6 months with the low-carbohydrate diet. A significant reduction in hemoglobin A_{1c} was observed across all dietary patterns at 6 months, ranging from -0.3% to -1%, compared with no dietary intervention. The largest hemoglobin A_{1c} reduction was achieved by the Mediterranean diet.³²

Intermittent fasting, as a nutritional approach, has gained traction in recent years, with various implementation patterns, including fasting every other day or for 2 consecutive days of the week. Time-restricted eating is a form of intermittent fasting that limits food intake to a specific window within a 24-hour period. It has been more widely adopted due to its relative ease of adherence compared with stricter fasting approaches.⁶ Intermittent fasting strategies lead to significant weight loss of 1.2 to 4 kg with favorable lipid profile changes, including lowering of total and LDL cholesterol and triglycerides. Alternate-day fasting has been associated with greater improvements in weight loss and lipid profiles compared with time-restricted eating.^{33,34} Despite ad libitum food intake during the eating time windows, caloric intake is lower with intermittent fasting and time-restricted eating, which at least partially explains the weight loss. Feeding windows of 8 hours or less have a greater weight advantage over longer eating windows.³⁵ Changes in diet-induced thermogenesis and protein and fat oxidation have also been implicated mechanistically.³⁶ The benefits of intermittent fasting have been linked to pleiotropic effects, including improvements in insulin sensitivity, cellular stress responses, anti-inflammatory activity, and regulation of the gut microbiota.³⁷ Time-restricted eating positively influences circadian rhythm and subcutaneous adipose tissue genes involved in metabolic regulation.³⁸ Time-restricted eating may also mitigate disordered eating behaviors, including late-night eating and irregular or prolonged eating windows.³⁹

Chrononutrition examines how the timing of food intake affects metabolic health and disease

risk. Breakfast intake has long been emphasized for successful weight management. Evidence from a 2008 study showed relatively lower weight gain with higher caloric intake at breakfast than at later times.⁴⁰ The weight-loss benefit associated with earlier time of eating is observed in isocaloric diets⁴¹ and may be lost if incorporating breakfast increases total caloric intake.⁴² Meta-analyses of randomized controlled trials suggest that consuming a larger share of daily calories earlier in the day, a strategy referred to as “front-loading,” promotes reductions in weight and waist circumference.³⁵ The correlation between metabolic outcomes and calorie distribution within a biological day remains inconclusive. Although studies have shown the advantage of early time-restricted feeding, namely from 7 AM to 3 PM, over a 12-hour feeding window, the variable metabolic and anthropometric outcomes might be related to the duration of the feeding window.⁴³ Standardizing the feeding time window would be needed to truly evaluate the effect of the timing of caloric intake.

Pragmatic Aspects of Implementation

An individual's preferences may affect adherence to the nutrition plan and, hence, remain central to the successful implementation of any dietary intervention. Dietary recommendations are more effective and better received when an individual's cultural background and readiness to change are considered. Socioeconomic status and access to food are key factors and should play a pivotal role in dietary conversations.⁴⁴ When developing individualized treatment plans, it is important to use mindful strategies to reduce weight bias and stigma in dietary discussions. While we delve into the nuances of nutritional strategies, it is important to recognize that broader challenges remain. For many individuals, ultraprocessed foods and caloric beverages have become entrenched in their day-to-day eating patterns. By affecting satiety and hunger sensation and increasing overall caloric intake, they foster

an unhealthy metabolic and obesogenic shift.⁴⁵ Incorporating awareness of these practical considerations supports better weight and metabolic outcomes with dietary interventions.

Clinical Case Vignettes

Case 1

A 46-year-old woman with a BMI of 34 kg/m² and weight-related comorbidities, including hypertension and prediabetes (hemoglobin A_{1c} = 6.1% [43 mmol/mol]), presents for discussion of weight management. She is perimenopausal with menstrual cycles occurring every 3 to 4 months. She currently skips breakfast, eats a light lunch, and has a larger evening meal around 9 to 10 PM due to work and caregiving responsibilities. She is concerned about rising fasting glucose and weight gain, despite eating less.

Which eating strategy could address this patient's concerns without changing the types of food or calorie targets?

- A. A consistent, earlier eating window (eg, 8-hour time-restricted eating)
- B. Very-low-carbohydrate diet with <50 g carbohydrate intake per day
- C. Mediterranean-style diet
- D. Calorie counting and maintaining a total caloric intake <1200 calories per day

Answer: A) A consistent, earlier eating window (eg, 8-hour time-restricted eating)

Evidence shows that shifting calorie intake to earlier in the day can improve weight outcomes, especially in individuals with late-night eating patterns. Answers B, C, and D involve changes in dietary composition, food types, and calorie targets and are therefore not suitable choices.

Case 2

A 58-year-old man presents with obesity (BMI = 35 kg/m²), type 2 diabetes (hemoglobin A_{1c} = 7.8% [62 mmol/mol]), hypertension, and dyslipidemia.

He reports multiple unsuccessful attempts to follow calorie-restricted diets. He enjoys cooking, prefers savory foods, and eats fish occasionally. His primary goal is to improve cardiometabolic health while adopting an eating pattern he can maintain long-term.

Which dietary recommendation best aligns with a Mediterranean dietary pattern and is most likely to improve his cardiometabolic risk?

- A. Emphasize low-fat packaged foods, avoid oils, and prioritize refined grains to reduce total calories
- B. Emphasize plant-focused meals with vegetables, legumes, whole grains, olive oil as the primary fat, moderate fish intake, and limited ultraprocessed foods
- C. Restrict carbohydrates to <10% of total calories and eliminate grains and legumes
- D. Use meal replacements twice daily with one calorie-controlled dinner

Answer: B) Emphasize plant-focused meals with vegetables, legumes, whole grains, olive oil as the primary fat, moderate fish intake, and limited ultra-processed foods

Plant-focused meals featuring vegetables, legumes, whole grains, olive oil as the primary fat, and moderate fish intake are consistent with the Mediterranean diet, which is associated with reduced cardiovascular risk. Low-fat, refined-carbohydrate-heavy patterns may worsen glycemic control and are less cardioprotective. Very-low-carbohydrate diets can be effective for some individuals but do not reflect a Mediterranean pattern and may limit sustainability. Meal replacements may support short-term weight loss but do not promote long-term changes in dietary patterns.

Case 3

A 49-year-old man presents with obesity (BMI = 37 kg/m²), a 6-year history of type 2 diabetes, hypertension, and hyperlipidemia. His current medications include metformin, a GLP-1 receptor

agonist, and basal insulin. His hemoglobin A_{1c} value is 8.9% (74 mmol/mol). He is interested in a high-fat, low-carbohydrate approach after seeing improvements in his family members who followed the same diet. He would like to understand how this will affect his cholesterol profile.

What are the lipid changes expected with a high-fat diet?

- A. Lower LDL cholesterol, lower HDL cholesterol, lower triglycerides
- B. Higher LDL cholesterol, higher HDL cholesterol, lower triglycerides
- C. Higher LDL cholesterol, higher HDL cholesterol, higher triglycerides
- D. No change in LDL cholesterol, HDL cholesterol, or triglycerides

Answer: B) Higher LDL cholesterol, higher HDL cholesterol, lower triglycerides

High-fat, low-carbohydrate diets usually decrease triglycerides and increase HDL cholesterol. A rise in LDL cholesterol is also observed, with the increase more pronounced in diets with higher saturated fat content.

Key Learning Points

- Macronutrient composition influences weight, satiety, and metabolic outcomes. Low- and very-low-carbohydrate diets can lower triglycerides, raise HDL cholesterol, and promote short-term weight loss, although LDL-cholesterol responses vary and long-term sustainability is limited. Adequate protein intake helps preserve lean mass during weight loss.
- Mediterranean and DASH dietary patterns provide durable cardiometabolic benefits. These nutrient-dense, plant-forward eating patterns consistently improve cardiovascular risk factors, with the Mediterranean diet showing the most sustained effects on LDL-cholesterol reduction, weight stability, and metabolic health.

- Meal timing and chrononutrition meaningfully affect metabolic regulation. Earlier eating windows, time-restricted eating, and front-loading calories can reduce weight and improve circadian alignment, even without changing calorie targets or food types.
- Intermittent fasting strategies support weight loss and metabolic improvements through

multiple mechanisms. Approaches such as alternate-day fasting and time-restricted eating reduce caloric intake, improve lipid profiles, and may influence circadian gene expression and inflammation.

- Personalization and addressing practical barriers determine real-world success.

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ADRENAL

New Management Options for Adults With Congenital Adrenal Hyperplasia

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Distinguish the complications observed in adults with congenital adrenal hyperplasia (CAH) due to the disease itself from those derived from long-term treatment with supraphysiological glucocorticoids (GCs).
- List the sites of action for non-GC adjunct therapies for CAH that have been studied and are in trials.
- Develop monitoring and GC-dose-reduction plans when adding adjunctive non-GC therapies in adults with CAH.

Significance of the Clinical Problem

Since Lawson Wilkins introduced cortisone therapy for children with classic CAH due to 21-hydroxylase deficiency (21-OHD) in the 1950s, GC therapy has been used both to replace cortisol deficiency and to normalize adrenal-derived androgens. In the absence of treatment, children

are at risk for adrenal crises with hypotension, hyperkalemia, and hypoglycemia. Chronically, the androgen and estrogen exposures cause rapid somatic growth with advanced bone age, precocious pubarche, short stature in adulthood, and derangements in both pubertal progression and fertility acquisition. Although replacement of daytime cortisol is conceptually simple, the poor pharmacokinetics of oral hydrocortisone, with peak circulating concentrations 1 to 2 hours after ingestion and a half-life of 60 to 90 minutes, lead at best to approximate replication of the normal circadian cortisol rhythm. Furthermore, higher-than-physiological doses are needed to normalize adrenal-derived androgens for several reasons: (1) the rise in ACTH and adrenal steroidogenesis starts at approximately 0400 prior to awakening and the first hydrocortisone dose; (2) the diversion of a massive steroid flux from approximately 7 mg/m² per day of cortisol generation to sex steroids, which are active at 100-times lower concentrations; and (3) the rapid clearance of oral hydrocortisone, which is proportionate to its concentration. While more potent synthetic GCs, such as prednisolone and its prodrug prednisone, methylprednisolone, and dexamethasone, can be used, these drugs have narrow therapeutic indices, and overtreatment can lead to growth suppression

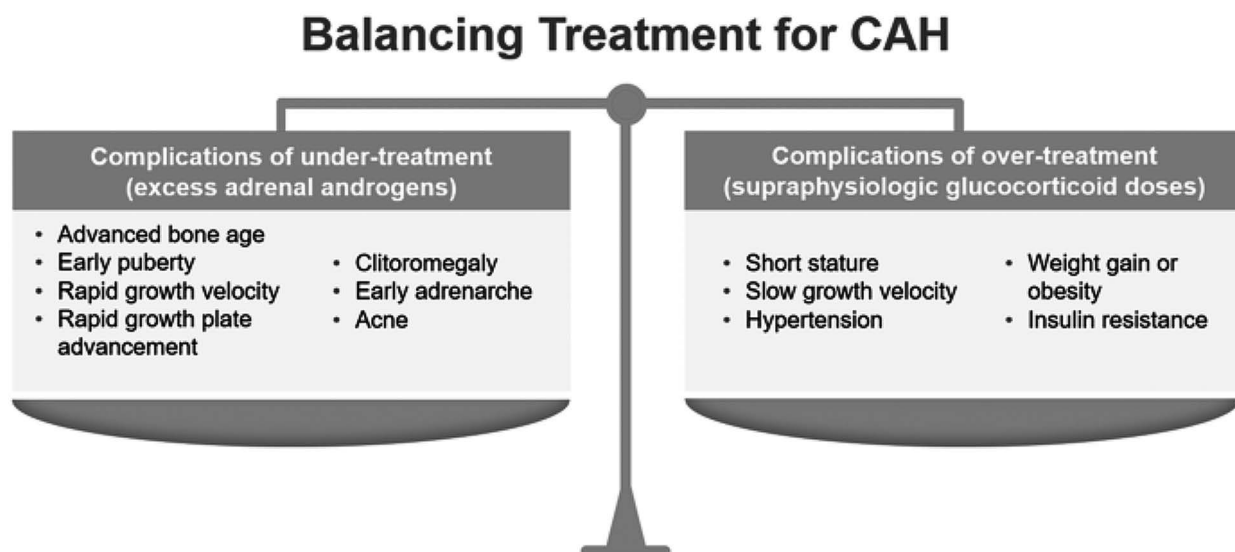
(Figure 1). Thus, pediatric care is a delicate balance between overtreatment and undertreatment, requiring frequent monitoring and dose adjustments and accounting for increasing body size over time.¹

Upon reaching adulthood, skeletal growth is completed, and well-managed adolescents with CAH will have completed pubertal maturation. Treatment intensity can be relaxed somewhat, given that gonadal-derived androgens are normally equal to or greater than the adrenal component in unaffected adults. Nevertheless, to achieve sufficient disease control to allow normal gonadal function, supraphysiological GC dosing is necessary for most patients. Cohorts of adults with CAH are observed to have a high prevalence of obesity, insulin resistance, low bone mineral density, and cardiovascular events,² very similar to what is observed in adults with subtle hypercortisolism from adrenal adenomas. Consequently, alternative approaches to reduce this excess GC exposure have been sought for both children and adults.^{3,4} This chapter reviews the management of men and women with CAH, using both traditional therapy and the implementation of non-GC adjunctive strategies.

Practice Gaps

- CAH is a rare disease, and patients rarely survived into adulthood before the 1970s, when hydrocortisone became widely available.
- Endocrinologists have little experience with the management of adults with CAH, the interpretation of biomarkers, and GC titration.
- Adults with CAH often get lost to endocrinology follow-up without a smooth transition from pediatric to adult care.
- GCs have narrow therapeutic indices, and long-term therapy leads to many complications, which take years to develop and vary substantially among individuals.
- Adults with CAH develop other diseases unrelated to their genetic condition, and delays in diagnosis and treatment often arise from “anchoring” on CAH as the reason for all their symptoms and findings.
- Adults with CAH are often weary of the disease burden and frustrated with the inability to find physicians who are comfortable managing CAH.

Figure 1. Balancing Treatment for Patients With CAH



Both overtreatment and undertreatment of CAH can lead to acute and chronic complications. Reprinted from Nokoff NJ et al. *J Clin Endocrinol Metab*, 2025; 110(Supplement 1): S13-S24. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

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Discussion

Deranged Steroid Production

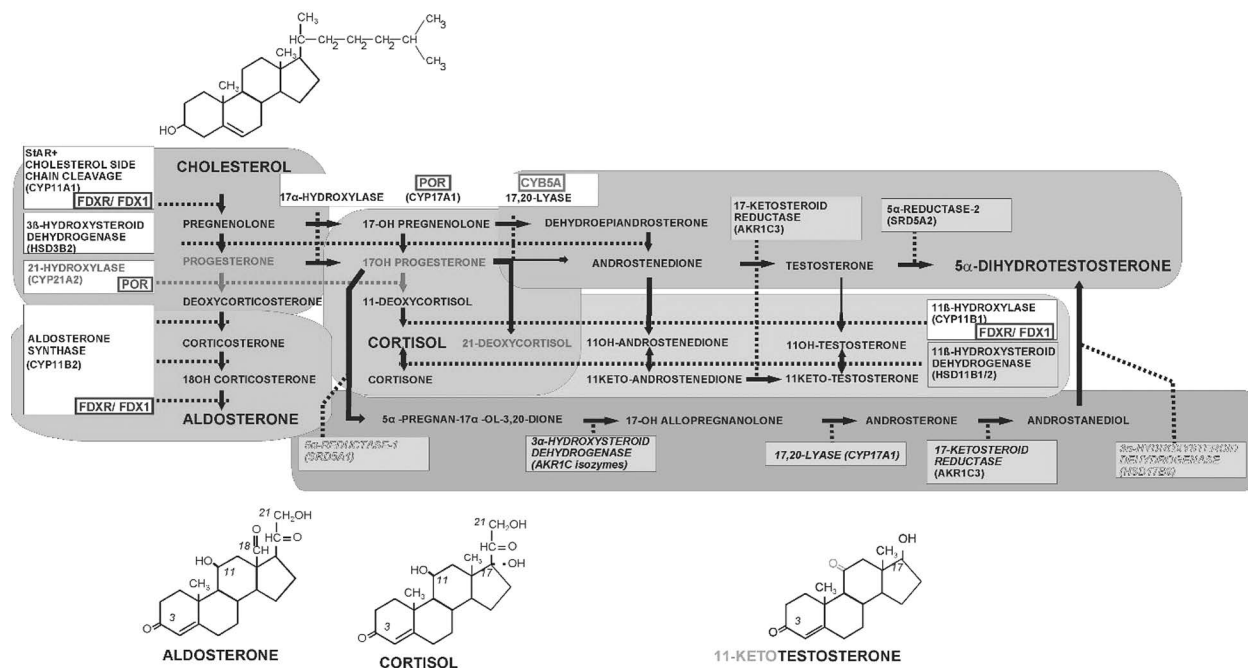
This chapter focuses on 21-OHD, the most common form of CAH. In 21-OHD, the block to cortisol and aldosterone synthesis reroutes steroid flux to androgens (*Figure 2*). The major steroid that accumulates above the block is 17-hydroxyprogesterone (17-OHP), which is used for diagnosis and, in children, for treatment monitoring. The adrenal glands produce the 19-carbon steroid androstenedione (A4), which is converted to the traditional androgens testosterone (T) and 5 α -dihydrotestosterone (DHT), primarily in extra-adrenal tissues. In addition, the adrenal-specific 11 β -hydroxylase enzyme (CYP11B1) converts A4 to 11 β -hydroxyandrostenedione (11-OHA4), which is converted in peripheral sites to the active androgen 11-ketotestosterone (11-KT) and its 5 α -reduced metabolite. In patients with 21-OHD, 11-OHA4 and 11-KT are often higher than A4

and T, respectively.⁵ Of note, individuals with other forms of CAH that feature androgen excess, such as 11 β -hydroxylase deficiency (11-OHD) and 3 β -hydroxysteroid dehydrogenase type 2 deficiency (3 β -HSD2D), produce very little 11-OHA4 and 11-KT, either because of 11-OHD or minimal intra-adrenal A4 synthesis, respectively. A final alteration worthy of recognition is that, upstream of 17-OHP, progesterone (P4) also accumulates, with no efficient intra-adrenal metabolic pathways, although some P4 is 11 β -hydroxylated in 21-OHD. Similar to synthetic progestins, P4 can suppress or alter the activity of the hypothalamic-pituitary-gonadal axis in both men and women, and in women, P4's action on the uterus is a major cause of irregular menses and infertility.

Traditional Treatment Strategies

Box 1 (following page) describes the stepped GC therapy for CAH. Corticosteroid replacement therapy for primary adrenal insufficiency involves

Figure 2. Pathways of Adrenal Steroidogenesis and Derangements in 21-OHD



The 17-hydroxyprogesterone that accumulates above the block can be converted to androgens via androstenedione and 11 β -hydroxyandrostenedione or, after 5 α -reduction, through the alternative pathway to 5 α -dihydrotestosterone. Progesterone also accumulates upstream of 17-hydroxyprogesterone. Reprinted from Claahsen-van der Grinten HL et al. *Endocr Rev*, 2022; 43(1): 91-159. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

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GC administration to approximate the circadian cortisol rhythm and fludrocortisone acetate as a substitute for aldosterone. Most hydrocortisone regimens use 2 or 3 daily doses with the largest dose on arising to mimic the early-morning cortisol peak. A second dose is added at or slightly after midday, and sometimes a third dose is taken in the late afternoon. The cortisol-vs-time curves derived from these regimens are not smooth replicas of normal individuals but rather jagged distortions with higher peaks and lower troughs throughout the day. Because the biological action of cortisol in cells persists for several hours after it is cleared from the circulation, patients fare reasonably well despite the deviation from ideal exposure. More potent synthetic GCs have longer half-lives than cortisol/hydrocortisone and are usually given once daily; however, their rapid absorption to peak and exponential clearance do not closely recapitulate normal cortisol dynamics. Fludrocortisone has a long half-life and acts by volume expansion over days to weeks; consequently, the effect is more chronic than acute, allowing for once- or twice-daily (or even alternate-day) dosing.

Box 1. Stepped GC Therapy for CAH

Step 1

- Hydrocortisone, 2-3 doses daily
- Largest dose on arising

Step 2

- Daytime hydrocortisone + bedtime long-acting GC
- (Methyl)prednisolone or prednisone, 0.5-3 mg at bedtime
- Or dexamethasone, 0.1-0.25 mg at bedtime

Step 3

- Twice-daily (methyl)prednisolone or prednisone
- Full replacement dose on arising 2-4 mg
- Minimum bedtime dose to control androgens ~20%-35% of morning dose

Step 4

- Once- or twice-daily dexamethasone
- Replacement dose on arising, minimum bedtime dose to goal
- Reserved for testicular adrenal rest tumors, need for rapid control
- Usually limited duration

The short half-life of hydrocortisone improves the safety profile relative to that of synthetic GCs, which have narrow therapeutic indices and are easily overdosed. In addition, traditional teachings and textbook tables typically scale GCs based on their anti-inflammatory activity rather than on their myriad other actions, including their effects on the hypothalamic-pituitary-adrenal axis. Hydrocortisone replacement was historically given as 20 + 10 mg daily in 2 doses, which is well above the daily cortisol production rate of $7 \pm 4 \text{ mg/m}^2$ per day, or about 15 mg daily total as is currently recommended. While traditional teaching also maintained that replacement with 15 to 20 mg of hydrocortisone equates to 5 mg daily of prednisone or prednisolone, a physiological dose is probably closer to 2.5 to 3 mg daily. Methylprednisolone is slightly more potent than prednisolone, and 2 mg daily is sufficient for many patients. For dexamethasone, even 0.25 mg daily can render patients cushingoid over months to years. Nevertheless, patients vary in their requirements, clearance, and tolerance of GCs, which mandates clinical judgment for dose titration.

Given the many considerations for corticosteroid replacement alone, the overproduction of adrenal androgens and precursors in CAH further complicates treatment. Although the between-dose troughs of hydrocortisone may be tolerated symptomatically, ACTH begins to rise when circulating cortisol falls below approximately $5 \text{ } \mu\text{g/dL}$ ($<140 \text{ nmol/L}$), which drives adrenal-derived androgen production.⁶⁻⁸ For these reasons, patients with CAH might have adequate replacement with nearly physiological GC dosing but have poor disease control. Longer-acting GCs and more frequent hydrocortisone dosing improve disease control; however, adverse effects increase as GC-free periods decrease, hindering recovery from the catabolic effects.

To titrate fludrocortisone, standing blood pressure, serum potassium and sodium, and plasma renin activity or mass are useful parameters (*Box 2, following page*). Fatigue that progresses throughout

the day and does not improve after a GC dose may be due to volume depletion and may respond to an increase in fludrocortisone. Conversely, hypokalemia, hypertension, and muscle cramps often indicate fludrocortisone overtreatment, especially when used in combination with hydrocortisone, which has some mineralocorticoid activity. A4 and T are the primary biomarkers used to titrate GC dosing, and 17-OHP is a highly sensitive marker of tight disease control, especially in children. Yet, 17-OHP varies more than A4 and T over time relative to the most recent GC dosing, which compromises its utility.

Box 2. Monitoring Parameters for 21-OHD

Men and women: mineralocorticoid dosing

- Standing blood pressure and heart rate (orthostatics)
- Serum potassium and sodium
- Plasma renin activity (or mass)

Men: GC dosing

- Serum T and SHBG (bioavailable testosterone) in normal male range
- Serum A4-to-T ratio <0.5
- Serum LH in normal range and LH > FSH
- Normal semen analysis if fertility desired
- Testicular ultrasonography to screen for testicular adrenal rest tumors

Women: GC dosing

- Clinical parameters: regularity of menses, hirsutism
- Serum testosterone and SHBG in or near-normal female range
- Serum A4 in or near-normal female range
- Serum follicular phase P4 <0.6 ng/mL (<2 nmol/L) when attempting to conceive

In men, LH and the A4-to-T ratio are useful parameters to assess testicular function. A low LH value indicates gonadal suppression from adrenal-derived sex steroids. LH can be suppressed when T is below or in the low end of the normal male range, because 11-KT is produced in excess of T in men with poorly controlled CAH. Only the Leydig cells express the *HSD17B3* gene, which encodes the 17- β HSD3 enzyme, the only enzyme that efficiently converts A4 to T. In postpubertal males, the A4-to-T ratio should be less than 0.5 (often <0.2). As adrenal-derived T increases, A4 increases

disproportionately, and the A4-to-T ratio rises. In men with high A4, 11-KT is also increased, and 11-KT is roughly inversely proportional to T in men with CAH.⁵ Elevated FSH can indicate irreversible Sertoli-cell damage, usually from testicular adrenal rest tumors (TARTs).⁹ A normal semen analysis is strong evidence of preserved testicular hormone and sperm production, but semen testing is ordinarily obtained only during an infertility evaluation.

TART development is a vexing problem in the management of boys and men with CAH. TARTs are derived from Leydig stem cells, which are reprogrammed under chronic ACTH stimulation to share some adrenal cortex properties. Thus, TART cells synthesize A4 and 11-OHA4 like the adrenal cortex but also higher relative amounts of T and 11-OHT directly, due to 17- β HSD3 expression.¹⁰ When boys reach adulthood, screening testicular ultrasonography is recommended; however, TARTs can develop much earlier, and more than half of boys and men with CAH have TARTs.¹¹ Small TARTs (<1 cm) generally do not interfere with testicular function but are a sentinel finding that should prompt close attention to disease control. Larger TARTs can impair blood flow into the normal testis, which is surrounded by a fibrous capsule, due to increased intratesticular pressure. This compromised blood supply can cause irreversible damage to the Sertoli cells and tubules. High-dosage GC regimens often shrink TARTs and can restore fertility,¹² although scar tissue from longstanding TARTs often remains. To regress TARTs, ACTH must be suppressed throughout the day using a regimen such as dexamethasone, 1 mg on arising and 0.5 mg at bedtime, or hydrocortisone, 10 mg 3 times daily with meals, plus dexamethasone, 0.25 mg at bedtime. Surgical removal of TARTs reduces mass effects, often permanently, but rarely restores testicular function.¹³ Thus, TART excision is reserved for patients in whom other options have been exhausted and/or fertility preservation is not desired.

For women, manifestations of androgen excess, such as facial hair, voice deepening, and

clitoral growth, are bothersome to many but not all patients. Consequently, a clinical assessment that aligns with the patient's goals is very important. Beyond these external manifestations, however, poor disease control can lead to eutopic adrenal and ectopic rest tumors in the pelvis. In particular, bilateral adrenal myelolipomas are not uncommon in men and women with poorly controlled CAH. These mesenchymal tumors are neither malignant nor steroid-producing, but treatment intensification rarely slows their growth. Very large tumors (>20 cm) commonly develop and cause mass effects, such as reflux, abdominal swelling, venous congestion, and discomfort lying prone. Surgical resection is feasible, but large tumors require open surgeries with large incisions and long recovery periods. After bilateral adrenalectomy, the corticosteroid insufficiency is very severe, and adrenal crises, which can result in death, become more common. Finally, these women require uterine protection from unopposed estrogen exposure during chronic anovulation, which can lead to endometrial hyperplasia and cancer. Elevated adrenal-derived P4 might mitigate some of this risk, as with progestin-eluting intrauterine devices, but the actual risk is unknown.

Adrenal-derived P4, which accumulates upstream of 17-OHP, is the main reason for irregular menses and infertility in women with CAH, similar to the spotting that occurs in unaffected women during progestin-only oral contraceptive therapy and depot medroxyprogesterone acetate treatment. Elevated P4 in the follicular phase of the cycle antagonizes estrogen-induced growth of the endometrial lining, changes gonadotropin pulsing to a pattern unfavorable for ovulation, and thickens cervical mucus, which prevents sperm penetration. These changes contribute to impaired ovulation, fertilization, and implantation. Although women with CAH can achieve normal fecundity rates with proper treatment regimens,¹⁴ the latency to pregnancy is longer than in unaffected women.¹⁵

Clinical Case Vignettes

Case 1

A 25-year-old woman with classic 21-OHD from birth presents for transition to adult care. CAH was well-managed with hydrocortisone until age 23 years, at which time her control began to deteriorate without any change in regimen. She has had amenorrhea for 6 months, oily skin, acne, and unwanted coarse hairs on her abdomen and chest. In addition, she is getting married and wants to start a family soon. Her current regimen consists of hydrocortisone, 10-10-5 mg with meals, plus fludrocortisone, 0.2 mg daily.

On physical examination, her blood pressure is normal. She has no cushingoid features, bruising, or muscle weakness. She has mild facial acne and oily skin.

Laboratory test results:

A4 = 490 ng/dL (<180 ng/dL) (SI: 17.1 nmol/L [<6.3 nmol/L])

T = 129 ng/dL (<60 ng/dL) (SI: 4.5 nmol/L [<2.1 nmol/L])

Which of the following changes to her regimen should be recommended to achieve pregnancy?

- A. No modification needed
- B. Increase hydrocortisone dosage to 10 mg 3 times daily with meals
- C. Add prednisolone, 2.5 mg at bedtime
- D. Add dexamethasone, 1 mg at bedtime
- E. Move the 5 mg dose of hydrocortisone to bedtime

Answer: C) Add prednisolone, 2.5 mg at bedtime

These data indicate very poor disease control, so treatment intensification is necessary (thus, Answer A is incorrect). A 5 mg hydrocortisone dose adjustment (Answers B and E) is unlikely to make much difference, given that she is already taking 3 doses daily. Dexamethasone (Answer D) would improve control but is contraindicated for pregnancy except under clinical trials, and 1 mg is an excessive

dose. A small dose of prednisolone at bedtime (Answer C) to reduce adrenal steroid production is both adequate and not excessive in most cases. An alternative would be twice-daily prednisolone, with a physiologic replacement dose in the morning (~3 mg) and enough at bedtime to achieve adequate control but not reverse circadian dosing, which is effective in achieving disease control but can impair sleep-wake cycles and cause metabolic deterioration. Methylprednisolone is a slightly more potent alternative to prednisolone. In the United States, generic methylprednisolone comes in 4-mg, 8-mg, and higher mg tablets. Prednisolone is available as 1 or 3 mg/mL liquid formulations or 5- and 20-mg tablets; however, the tablets are now very expensive. Prednisone is a prodrug of prednisolone, which is converted in the liver, but the kinetics of active drug exposure are slower and less consistent than prednisolone. Prednisone comes in many dose sizes, as low as 1-mg tablets.

Case 1, Continued

Her regimen was modified with the addition of prednisolone, 2.5 mg at bedtime. In 3 months, monthly menses resumed.

Which of the following laboratory parameters is most important for achieving pregnancy?

- A. Early-morning A4 in normal range
- B. Pre-GC dose testosterone <30 ng/dL (SI: <1 nmol/L)
- C. Mid-day 17-OHP <1000 ng/dL (SI: <30 nmol/L)
- D. Cycle-day 21 A4-to-testosterone ratio <0.5
- E. Follicular-phase morning P4 <0.6 ng/mL (SI: <2 nmol/L)

Answer: E) Follicular-phase morning P4 <0.6 ng/mL (<2 nmol/L)

Retrospective studies from University College of London have demonstrated that a follicular-phase P4 concentration less than 0.6 ng/mL (<2 nmol/L) (Answer E) is a reliable target¹⁴ for medication

titration in women with CAH who are attempting to conceive—even 1 ng/mL (3 nmol/L) is sufficient in many cases. Often, these pregnancies are achieved after adding a bedtime dose of prednisolone to block the early-morning rise in ACTH, 17-OHP, and P4. In many cases, a smaller dose of 0.5 to 2 mg is adequate, depending on antecedent control. Answers A through D are incorrect, as no other biomarkers are helpful in GC titration to achieve pregnancy, although changes in the various steroids generally correlate with one another.

Repeat testing showed:

A4 = 170 ng/dL (SI: 6 nmol/L)
 T = 35 ng/dL (SI: 1.2 nmol/L)
 P4 = 0.5 ng/mL (SI: 1.6 nmol/L)

Thus, her treatment was targeted to goal.

This regimen, however, was too complicated for her, and the prednisolone tablets had become very expensive and were not covered by her insurance. Her regimen was changed to methylprednisolone, 6 mg in the morning only, and the repeat follicular-phase P4 measurement was 2.2 ng/mL (7 nmol/L) despite A4 and T in the normal female range. Thus, a 2-mg dose of methylprednisolone was added at bedtime, and the follicular-phase P4 concentration fell to 1.2 ng/mL (4 nmol/L). On physical examination, however, she had developed violaceous striae, skin thinning, and bruising, and she had gained 35 lb (16 kg). With shared decision-making, a break from the potent methylprednisolone was initiated, and her GC was changed to hydrocortisone, 10 mg 3 times daily. With this change, she promptly felt better and started to lose weight. In 6 weeks, however, her amenorrhea recurred, with fatigue and leg edema. A pregnancy test was positive, and she carried a healthy girl to term (cesarean delivery). She had a second child and is now pregnant with her third.

This case illustrates that once tight control is achieved, it is easier to maintain with lower-dosage regimens that might have been previously ineffective. Most likely, this phenomenon is due to adrenal cortex atrophy and a reduced mass of steroid-producing cells after treatment intensification.

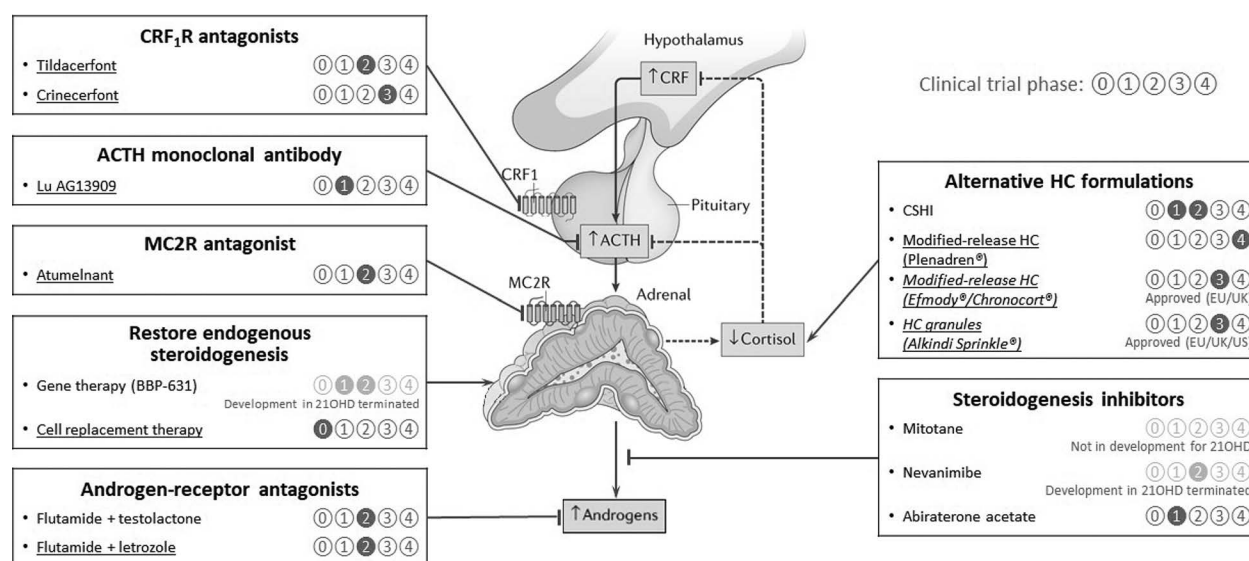
Non-GC Treatment Options

Women with nonclassic 21-OHD do not have clinically manifest adrenal insufficiency and thus do not require GC therapy. GC treatment is used for children with advancing bone age to delay skeletal maturation and to optimize adult height. Upon reaching adulthood, these women are often treated with spironolactone and estrogen-containing oral contraceptives to mitigate the unwanted androgen actions and to restore cyclic menses. If menses are regular in adulthood, no therapy is mandatory, and hirsutism can be managed with mechanical epilation or topical eflornithine cream (which is no longer in production and must be compounded now). In fact, one case series described 3 children with nonclassic 21-OHD who achieve predicted adult height with aromatase inhibitor monotherapy (anastrozole).¹⁶ The National Institutes of Health conducted a randomized controlled trial comparing conventional hydrocortisone therapy (15 mg/m² per day) with reduced-dose hydrocortisone (7.6 mg/m² per day) plus an antiandrogen and an aromatase inhibitor in 62 children, 45 of whom completed the study. Adult heights were not higher with the experimental

regimen but were not lower,¹⁷ demonstrating proof-of-concept that non-GC medications might be used in patients with CAH to limit excessive exposure to exogenous GCs.

To apply these principles to adults with classic 21-OHD, the major difference is that these patients experience cortisol (and often aldosterone) deficiency, and GC therapy should not be stopped completely. Supraphysiological GC doses (often 15–17 mg/m² per day), however, are typically required to achieve a degree of disease control sufficient to maintain fertility and to prevent adrenal (and rest) tumor formation. In large observational studies from the United Kingdom¹⁸ and the National Institutes of Health¹⁹ in the United States, adults with classic CAH have a high prevalence of comorbidities that are typical of overexposure to GC, including obesity, glucose intolerance, adverse cardiovascular risk and events, reduced bone mass, and mental health treatments. Thus, the logic of non-GC therapies is based on the hypothesis that reducing GC exposure will mitigate these adverse comorbidities. However, to maintain disease control, non-GC drugs that attack other targets are needed, as shown in *Figure 3*.^{3,4}

Figure 3. Targets of Non-GC Therapies for CAH



Since this publication, both Lu AG13909 (asdebart) and atumelnant have advanced to phase 2 and 3 trials in adults, with a phase 3 trial of atumelnant in children. Crinecerfont is in phase 3b and 4 trials, and the phase 1 trial of abiraterone acetate has been terminated. Reprinted from Sarafoglou K & Auchus RJ. *J Clin Endocrinol Metab*, 2025; 110(Supplement 1): S74-S87. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

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Before discussing non-GC therapies, an alternative approach is to improve the pharmacokinetics of hydrocortisone by reducing the wide exposure swings from tablets, either by altering the formulation or the route of delivery. Hydrocortisone hemisuccinate is the more water-soluble ester of hydrocortisone used for parenteral administration (Solu-cortef). This solution can be administered using a programmable (insulin) pump to replicate the normal circadian pattern more smoothly than tablets and without interdose nadirs and the associated rise in ACTH. Small series²⁰ have consistently shown improved disease control with continuous infusion at the same total daily dose as tablets, especially in patients with rapid cortisol clearance.²¹ Although effective and flexible, subcutaneous hydrocortisone hemisuccinate administration via an insulin pump is expensive, off-label, labor-intensive, and prone to mechanical failures and infusion-site reactions. This approach is impractical for most patients with CAH but remains an option for highly motivated patients.

Nevertheless, these studies of continuous hydrocortisone hemisuccinate delivery provided proof of concept, which inspired the development of modified-release oral hydrocortisone (MR-HC) formulations. Efmody (Neurocrine Biosciences) is microgranules of hydrocortisone around an inert core particle with an enteric coating that is supplied in 5-, 10-, and 20-mg capsules. The enteric coating delays absorption for 2 to 4 hours and produces a broad peak with a gradual decline over 12 to 16 hours. The morning exposure is dosed at bedtime, providing some circulating cortisol before awakening, and a second, smaller dose is given on arising to maintain cortisol levels into the evening. Note that MR-HC pharmacokinetics are *not* the same as prednisolone, which, like hydrocortisone, also features a rapid peak and exponential decay, but with a longer half-life than hydrocortisone. Compared with tablets, this MR-HC achieved better disease control in the early-morning hours at a similar dose of 30 to 32 mg daily (15–17 mg/m² per day).²² After the 6-month formal blinded comparison phase,

investigators gradually reduced the MR-HC dose to approximately 20 mg daily (11 mg/m² per day) and maintained good disease control, with only moderately elevated 17-OHP levels. Good disease control was maintained for years during long-term follow-up studies.²³ Anecdotally, some women with infertility—despite intensive control with conventional therapy—conceived using MR-HC. MR-HC (Efmody hard capsules) is approved by the European Medicines Agency for the treatment of classic CAH and is available in several European countries. While the more efficient exposure from equivalent daily doses of MR-HC improves disease control over hydrocortisone tablets, weight gain was commonly observed with this treatment. Thus, both the positive and negative effects of hydrocortisone can be amplified by the modified formulation. Patients who can achieve good disease control with a lowered total dose of GC can benefit significantly from long-term therapy with MR-HC.

Abiraterone Acetate

Abiraterone acetate (AA) is the oral formulation and prodrug for abiraterone, a potent and very specific inhibitor of CYP17A1 (steroid 17-hydroxylase/17,20-lyase), which is the enzyme required for conversion of 21-carbon precursor steroids (including 17-OHP) to 19-carbon products, which are proximate intermediates in androgen biosynthesis (*Figure 2*). In a small study of 6 adult women with CAH who were taking oral contraceptives and hydrocortisone (20 mg daily), AA at a dosage of 100 to 250 mg daily for 6 days consistently reduced A4, T, and urine androgen metabolites into the normal range during day 6, and these biomarkers remained well below baseline 48 hours after the final dose.²⁴ A trial of AA in prepubertal children was initiated but not completed for logistical reasons. Nevertheless, AA has been used to effectively improve disease control for short periods in difficult-to-manage CAH in adults.²⁵ AA would not be suitable for long-term management in adults, because the drug also inhibits gonadal androgen (and thus estrogen) production and increases progesterone accumulation.²⁶

Crinecerfont

When the first of 2 receptors for corticotropin-releasing hormone (or factor, the type 1 receptor referred to as CRF₁), its expression in the pituitary corticotropes was confirmed as anticipated.

Unexpectedly, CRF₁ was also found to be widely distributed in the cerebral cortex. In addition, the CRF₁-null mouse was resistant to anxiety-like behaviors, which spurred the development of CRF₁ antagonists for the treatment of mood disorders. Although some benefit was observed in clinical trials, the drugs did not appear more promising than selective serotonin reuptake inhibitors, and the programs were terminated. In the mid-2010s, some of these compounds were repurposed for the pituitary-directed treatment of CAH.^{27,28} Phase 2 and 3 studies of crinecerfont in children^{29,30} and adults^{31,32} with CAH demonstrated a reduction in A4, which subsequently enabled a reduction in GC dosing. Based on these trial results, the US Food and Drug Administration approved crinecerfont as an adjunctive therapy for children (4 years and older) and adults with CAH. The adult dosage is 100 mg twice daily with meals, and the total daily dose is increased to 300 or 400 mg in patients taking moderate or potent CYP3A4-inducing drugs, respectively (eg, rifampin). In children, weight-based dosing is used: 10 to 20 kg, 25 mg twice daily; 20 to 55 kg, 50 mg twice daily; >55 kg, 100 mg twice daily. Crinecerfont is available in 25-, 50-, and 100-mg hard gelatin capsules, as well as a 50 mg/mL oral solution.

Only a minority of children and adults with CAH can maintain desired disease control with physiological dosing of hydrocortisone. The recommended use of crinecerfont is to achieve that target control with approximately physiological GC exposure, to mitigate both short- and long-term complications. Crinecerfont is typically added either when patients are unable to achieve desired disease control, based on biomarkers (eg, A4 and 17-OHP) and clinical parameters, despite the maximal tolerated GC dose (which is also clinically determined), or when adequate disease control is achieved at the expense of clinical and objective manifestations of GC toxicity, such as weight gain,

glucose intolerance, skin thinning, myopathy, poor sleep, easy bruising, and low bone density. Data from the phase 3 trials have shown weight loss, improved insulin sensitivity, and activation of suppressed bone turnover, which are consistent with the effects of the GC dose reduction.^{30,31}

Before starting crinecerfont, patients should be educated about GC withdrawal symptoms, and targets for disease control and ultimate GC dosing should be set through shared decision-making. In patients with very suppressed adrenal function from dexamethasone, high-dose prednisolone, or combination therapy who wish to transition to hydrocortisone, GC transitioning commonly precipitates prominent withdrawal symptoms. Consequently, for these patients, conversion to a roughly equivalent dose of hydrocortisone (such as 10 to 15 mg 3 times daily) is advisable before starting crinecerfont, which is not started until GC withdrawal symptoms have abated. Due to adrenal atrophy, these patients usually stay in tight control for many months during this conversion, so a delay is not critical. In patients with moderately high doses of hydrocortisone and/or prednisolone (~15-17 mg/m² per day hydrocortisone or its equivalent, as is typical), crinecerfont is simply added, and GC dosing is not changed for at least 4 weeks, at which time repeat biomarker data are obtained. The poorer the disease control before starting crinecerfont, the longer one should wait before starting GC dose reduction. GC reduction should be gradually achieved in small increments, such as reducing hydrocortisone by 2.5 mg daily or prednisolone by 0.5 mg daily, and not more frequently than every 4 weeks. In the phase 3 trial in adults, the most toxic and nonphysiological (yet most effective in controlling androgen excess) doses were reduced first, with the goal of approaching circadian cortisol exposure,³¹ and the approach in clinical use should be similar. Thus, bedtime GCs are tapered and discontinued first, and daytime dosing is adjusted as in autoimmune or iatrogenic primary adrenal insufficiency. The rate of GC reduction is based primarily on the presence and severity of GC withdrawal symptoms and predicated on achieving or maintaining

target biomarker control, and subsequent dose reductions should not be attempted without confirming that biomarkers and clinical parameters remain at previously articulated goals.

In addition, primarily for patients taking hydrocortisone as their only GC, a dose adjustment (increase) in fludrocortisone might be necessary during hydrocortisone tapering. Conversely, patients who are managed with prednisolone or dexamethasone might need a fludrocortisone dose reduction when transitioning to hydrocortisone. Once the target GC dose reduction is achieved, patients should be monitored periodically to ensure sustained efficacy, using clinical and biomarker parameters. Finally, stress dosing instructions should be frequently reviewed and clearly articulated during GC dose reduction. A hydrocortisone dose of 15 to 17 mg/m² per day is already a 2- to 3-times physiological “stress dose” for minor illnesses that are managed at home. For example, a patient whose dose is tapered to a single dose of hydrocortisone, 10 to 15 mg on arising, should not only increase the total dose but also distribute it throughout the day (eg, 10 mg 3 times daily) during illness. Injectable hydrocortisone hemisuccinate up to 100 mg should be available for significant illness, when the patient cannot take oral GCs and needs immediate GC exposure during transportation to a medical facility for urgent care.

Case 2

A 22-year-old woman with classic 21-OHD has transitioned to adult care taking hydrocortisone, 12.5/10/10 mg with meals, and fludrocortisone, 0.1 mg daily. She reports no recent weight gain, easy bruising, or muscle weakness. However, she has not had menses for a year, and she plucks terminal hairs on her chin weekly. The absence of menses concerns her, as she plans to have children in the future. She finds the facial hair tolerable but unpleasant.

Laboratory test results:

A4 = 480 ng/dL (SI: 16.8 nmol/L)
T = 195 ng/dL (SI: 6.8 nmol/L)

P4 = 3.2 ng/mL (SI: 10.2 nmol/L)
Plasma renin = 77 pg/mL (SI: 1.8 pmol/L)
Potassium = 4.7 mEq/L (SI: 4.7 mmol/L)

Her hydrocortisone regimen is simplified to 10 mg 3 times daily. Prednisolone, 1 mg, is added at bedtime and increased to 3 mg, and fludrocortisone is increased to 0.2 mg daily.

Repeat testing showed:

A4 = 808 ng/dL (SI: 28.3 nmol/L)
T = 119 ng/dL (SI: 4.1 nmol/L)
Plasma renin = 88 pg/mL (SI: 2.1 pmol/L)
Potassium = 4.0 mEq/L (SI: 4.0 mmol/L)

At her follow-up visit, she has developed slight subcutaneous fat pads and facial plethora and rounding. She has no bruising or muscle weakness. She had menses once after increasing the prednisolone dose to 3 mg at bedtime.

You are concerned that she is becoming cushingoid and is at risk for metabolic complications.

Which of the following options would best reduce her GC exposure while maintaining control of her CAH?

- Discontinue bedtime prednisolone
- Add crinecerfont, 100 mg twice daily
- Change hydrocortisone dose to 7.5 mg 4 times daily
- Move prednisolone to the morning
- Change prednisolone to dexamethasone, 0.5 mg at bedtime

Answer: B) Add crinecerfont, 100 mg twice daily

Answers A, C, and D either reduce or continue the same dose of GC, and the bedtime prednisolone is the most important in her current regimen for maintaining disease control. While dexamethasone might be more effective than prednisolone, the dose of 0.5 mg daily (Answer E) is roughly 3 times the GC exposure as 3 mg of prednisolone, which will exacerbate her iatrogenic Cushing syndrome. The addition of crinecerfont (Answer B) has been shown to allow for GC dose reduction while maintaining disease control.

Case 2, Continued

Crinecerfont is added to the patient's regimen, and she tolerates it well. She has had monthly menses since starting crinecerfont, and her facial hair has become finer, requiring less frequent grooming.

After 4 months, the following laboratory test results are obtained:

A4 = 274 ng/dL (SI: 9.6 nmol/L)
 T = 41 ng/dL (SI: 1.4 nmol/L)
 Plasma renin = 64 pg/mL (SI: 1.5 pmol/L)
 Potassium = 4.6 mEq/L (SI: 4.6 mmol/L)

Which of the following is the best way to start tapering her GC therapy?

- Change regimen to hydrocortisone only, 15 mg on arising and 5 mg in the early afternoon, in 1 step
- Discontinue prednisolone and change hydrocortisone to 15 mg on arising and 5 mg in the early afternoon 2 weeks later
- Discontinue hydrocortisone
- Reduce prednisolone from 3 to 2 mg and repeat laboratory testing in 4 to 6 weeks
- Stop midday hydrocortisone and repeat laboratory testing in 6 months

Answer: D) Reduce prednisolone from 3 to 2 mg and repeat laboratory testing in 4 to 6 weeks

Now that T is normal and A4 is nearly normal, the options are to continue without any changes and repeat testing in another 2 to 3 months (not given as an option) or to begin a gradual taper, starting with the most nonphysiological GC dose. Answers A, B, and C involve large and rapid dose reductions, which are likely to either precipitate GC withdrawal symptoms or lead to worsening disease control. Answer E might be reasonable if the patient has difficulty remembering the midday dose, but 6 months is too long to wait until repeating testing to assess response to this change. The best option is to reduce the prednisolone dose by 1 mg and repeat testing in less than 2 months (Answer D) to confirm that disease control has

not deteriorated. Given the marked reduction in A4 and T, it is likely that some adrenal atrophy has occurred, requiring several months of dose intensification.

The patient was unable to get repeat testing done for 4 months, at which time the following was documented:

A4 = 69.5 ng/dL (SI: 2.4 nmol/L)
 T = 25.2 ng/dL (SI: 0.88 nmol/L)
 Plasma renin = 20 pg/mL (SI: 0.5 pmol/L)
 Potassium = 4.6 mEq/L (SI: 4.6 mmol/L)

The bedtime prednisolone was decreased to 1 mg and discontinued 4 weeks later. Although the intervals between laboratory tests were longer than necessary due to the patient's work schedule, the extended period with both crinecerfont and high (but previously inadequate) GC exposure allowed successful restoration of menses and biomarker targets without GC withdrawal symptoms or loss of disease control. Lesson: err on the side of slower rather than faster!

The key principles of GC reduction after starting crinecerfont can be summarized as:

- Wait until biomarkers are at or near goal before tapering.
- Allow sufficient time for adrenal atrophy; the higher the biomarkers, the longer this process will take.
- Start with the most nonphysiological GC doses and make small reductions over several months to avoid withdrawal symptoms.
- Confirm that biomarkers and clinical parameters remain at target before subsequent GC reductions.

Additional Trials and New Medications

Crinecerfont is being trialed in children younger than 4 years, and long-term observational studies are in progress, with additional studies in planning. Only a fraction of the data from the phase 3 trials have been fully evaluated and published, with more information forthcoming. In addition, the crinecerfont labeling states that the drug is "indicated as adjunctive treatment to GC replacement to control androgens in

adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH),” without specification of 21-OHD—the exclusive form of CAH studied in the clinical trials. Consequently, patients with classic 11-OHD have been treated with crinicerfont as a part of usual clinical practice, and some information on its effectiveness for this form of CAH is beginning to emerge.

Atumelnant is a small-molecule antagonist of the melanocortin type 2 (ACTH) receptor (MC2R), which has completed phase 1 and 2 studies and is now in phase 3 trials for both children and adults with CAH. Atumelnant is taken orally once daily. A humanized anti-ACTH antibody, Lu AG13909 (asedebart) has fully enrolled its phase 1 studies in Europe and is in a phase 2 trial of different dose cohorts with monthly infusions. A gene therapy trial (BBP-631) was started but terminated when the highest dose did not afford sufficient cortisol production to justify further development.⁴

Key Learning Points

- Chronic exposure to elevated ACTH and adrenal-derived androgens can lead to eutopic adrenal and ectopic rest tumor formation and to infertility in men and women with CAH.

- Supraphysiological GC doses are commonly required to maintain adequate disease control to prevent these complications.
- Chronic exposure to supraphysiological GC doses increases the risk of additional long-term morbidities related to cardiovascular, metabolic, bone, and mental health.
- Cortisol replacement with daytime GC and mineralocorticoid as needed is recommended throughout life, with stress dosing for illness.
- Adrenal-derived P4 is the major cause of infertility and irregular menses in women with CAH, and it is the parameter to most closely monitor in women with CAH who are trying to conceive.
- In men with CAH, an A4-to-T ratio less than 0.5 and nonsuppressed LH are consistent with adequate disease control, allowing normal testicular function.
- Non-GC therapies, such as crinicerfont, a CRF1 antagonist, have been developed to allow GC dose reduction while maintaining the desired degree of disease control.

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Adrenal Aftermath: Postoperative Adrenal Insufficiency and Glucocorticoid Withdrawal Syndrome After Surgery for Cushing Syndrome

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the clinical scenario of postoperative adrenal insufficiency after curative surgery for endogenous Cushing syndrome.
 - Guide the management of postoperative adrenal insufficiency and glucocorticoid withdrawal syndrome (GWS).
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Significance of the Clinical Problem

Cushing syndrome is a state of chronic glucocorticoid excess that results in severe clinical manifestations, long-term morbidity even after treatment, and increased mortality. Endogenous hypercortisolism causes classic somatic features, and when severe, it contributes to cardiometabolic diseases (eg, hypertension, hyperglycemia, dyslipidemia, cardiovascular diseases, and thromboembolism), musculoskeletal impairment (eg, myopathy, osteoporosis, and fractures), and neurocognitive and psychiatric manifestations, eventually leading to disability and reduced quality of life.

The treatment of Cushing syndrome depends on the etiology and relies on surgical approaches or medical therapies. First-line management is surgical whenever possible, and includes resection of the primary tumor (pituitary, adrenal, or ectopic). If surgery is unsuccessful, second-line options include repeated surgery, radiotherapy, or bilateral adrenalectomy. Medical therapy can be used for selected patients as a bridge before surgery or when surgical resection is incomplete or not feasible.

After successful treatment, the abrupt transition from chronic supraphysiologic cortisol exposure to relative cortisol deficiency requiring replacement frequently precipitates postoperative adrenal insufficiency and may trigger GWS. Adrenal insufficiency results from prolonged suppression of the hypothalamic-pituitary-adrenal (HPA) axis and reduced adrenal reserve. GWS encompasses a complex of neuropsychiatric symptoms that may be observed during the tapering or withdrawal phase of glucocorticoid replacement treatment, overlapping those of adrenal insufficiency.

The recognition and clinical management of those conditions are key to clinical practice and pose a challenge for physicians.

Practice Gaps

- Risk prediction remains imprecise for postoperative adrenal insufficiency and the timing of recovery, particularly in cases of mild autonomous cortisol secretion (MACS).
- Postoperative testing pathways are heterogeneous (in timing, cutoffs, and test types), limiting comparability and the development of unified algorithms.
- Evidence-based tapering protocols are lacking, especially when severe GWS symptoms emerge, such as psychiatric decompensation.
- Additional management of GWS is supported conceptually but remains underinvestigated.

Discussion

Postoperative Adrenal Insufficiency

Postoperative adrenal insufficiency is an expected consequence of remission after surgical treatment for endogenous hypercortisolism, often beginning immediately after curative surgery. It remains prevalent across the entire spectrum of hypercortisolism, with its duration largely driven by disease severity. Postoperative adrenal insufficiency is expected in patients with Cushing disease who achieve remission after transsphenoidal surgery, when early postoperative hypocortisolism is used as the remission criterion. In the largest systematic review of unilateral adrenalectomy outcomes, postoperative adrenal insufficiency occurred in 99.7% of patients with overt Cushing syndrome and in 65.3% of those with MACS.¹ However, data on the prevalence of adrenal insufficiency after curative surgery for MACS have been limited by different definitions adopted before the first European guidelines published in 2016, revised in 2023.^{2,3} More recent series applying a guideline-based definition of MACS show rates of adrenal insufficiency ranging from 23% to 55%, depending on the postoperative assessment of adrenal insufficiency and the indication for surgery.⁴⁻⁶ Assessment of postoperative adrenal insufficiency is not yet

standardized. Although empiric glucocorticoid coverage can be offered to all patients with Cushing syndrome, due to the high probability of having postoperative adrenal insufficiency, more tailored approaches have been proposed to avoid unnecessary glucocorticoid treatments. In patients with Cushing disease who are not receiving glucocorticoids perioperatively, an expected drop in serum cortisol levels (usually $<5 \mu\text{g/dL}$ [$<138 \text{ nmol/L}$] within the first 24-48 hours) suggests remission and supports initiation of glucocorticoid replacement therapy.⁷ Some centers use consecutive serum cortisol values less than $3 \mu\text{g/dL}$ ($<83 \text{ nmol/L}$) to define successful tumor resection and start glucocorticoid therapy.⁸ In patients with hypercortisolism due to adrenal diseases, especially MACS, a morning serum cortisol value less than $10 \mu\text{g/dL}$ ($<276 \text{ nmol/L}$) on postoperative day 1 supports the diagnosis of adrenal insufficiency.^{5,9} Recent data analyzing the performance of dynamic testing after surgery show that cosyntropin-stimulation testing on postoperative day 1 might be preferred to basal cortisol measurement on postoperative day 1 to identify patients at risk of secondary adrenal insufficiency after surgical treatment of MACS.¹⁰ The guidelines from the American Association of Endocrine Surgeons recommend empiric postoperative glucocorticoid replacement therapy for all patients with Cushing syndrome after unilateral adrenalectomy, leaving the morning cortisol measurement on postoperative day 1 or dynamic testing for patients with MACS.¹¹

Patients with postoperative adrenal insufficiency are at increased risk of adrenal crises, with an incidence of 9.0 crises per 100 patient-years, occurring in a median time of 2 months (interquartile range, 1-22 months) since the last surgery.¹² Therefore, structured patient and caregiver education, including an explanation of sick-day rules, should be part of both preoperative and postoperative assessments. Reinforcing emergency management behaviors and intensification of follow-up are also required after a first adrenal crisis, given the high risk of subsequent crises.

Recovery of the HPA Axis After Curative Surgery for Cushing Syndrome

Functional recovery of the HPA axis is a stepwise process that occurs after curative surgery for Cushing syndrome, with prolonged HPA-axis suppression and adrenal atrophy as contributing factors, depending on the etiology. Large clinical studies have shown a median time to recovery of normal cortisol secretion of 1.4 to 2.1 years for Cushing disease, 0.6 years for ectopic Cushing syndrome, 0.9 to 2.5 years for adrenal Cushing syndrome, and 0.2 to 0.5 years for patients with MACS.^{1,13-21} The significant variability observed in some categories may be influenced by several biological factors, such as the duration and severity of hypercortisolism, which affect the length of HPA-axis recovery. However, differences in tapering schemes (possibly also due to concomitant GWS), timing and modality of assessing HPA-axis recovery, and varying diagnostic criteria in some forms of hypercortisolism (ie, MACS, especially in older studies published before the European guidelines) are important contributors to the variable duration of glucocorticoid replacement after surgery. In a recent study investigating the full spectrum of hypercortisolism, the rates of HPA-axis recovery were 40% at 1 year, 73% at 2 years, and 83% at 5 years. The median time to recovery of adrenal function was 14 months.¹⁹ Recovery was high overall but slightly lower in Cushing disease compared with adrenal Cushing syndrome at 5 years (81% vs 91%, respectively). Long-term data show that some patients might not recover a functional HPA axis at all and may require long-term glucocorticoid replacement therapy, especially those with Cushing disease who have impairment of more than 1 pituitary axis after surgery.¹⁹

Postoperative assessment of HPA-axis recovery is not yet standardized regarding the management of glucocorticoid treatment and tapering schemes. A widely accepted definition of HPA-axis recovery is a morning serum cortisol concentration of 10 µg/dL or greater

(≥276 nmol/L) or a cortisol concentration after cosyntropin-stimulation testing of 18 µg/dL or greater (≥500 nmol/L) (the latter in case of a morning cortisol value of 2 to 10 µg/dL [55-276 nmol/L]).^{9,20,21} It is important that those measurements are done at least 24 hours after the last glucocorticoid dose, provided that short-acting (eg, hydrocortisone and cortisone acetate) or intermediate-acting glucocorticoids (ie, prednisone and prednisolone) are used. The Endocrine Society guidelines suggest assessing morning cortisol every 3 months, followed by cosyntropin-stimulation testing when the concentration is 7.4 µg/dL or greater (≥200 nmol/L). Patients with cortisol concentrations below 5 µg/dL (<138 nmol/L) should be advised to continue glucocorticoid treatment until retesting in 3 to 6 months. Stimulation testing may be helpful in patients with intermediate morning cortisol values. However, it must be recognized that these are not clear-cut recommendations and that clinical judgment should guide any decision in this context.²²

Glucocorticoid Withdrawal Syndrome

GWS is characterized by a series of symptoms emerging after a rapid reduction in cortisol exposure after curative surgery for Cushing syndrome. Although the pathogenesis remains to be established, possible mechanisms include reduced sensitivity to glucocorticoids, downregulation of corticotropin-releasing hormone (CRH) and proopiomelanocortin (POMC) expression, and a proinflammatory state.²³ GWS might be precipitated by attempts to taper glucocorticoid replacement therapy, even at supraphysiological doses. The clinical picture is characterized by fatigue, myalgias, arthralgias, and mood symptoms that resemble those of adrenal insufficiency, ultimately leading to reduced quality of life. Distinguishing between the 2 conditions is clinically challenging, even though certain features may favor one diagnosis over the other (*Table, following page*).^{8,24} In the first weeks after remission, commonly reported symptoms include

myalgias and arthralgias, fatigue, weakness, sleep disturbance, headaches, and mood changes, with several symptoms persisting in the early postoperative period and some (notably pain and fatigue) becoming more predominant later in recovery.²⁴ Beyond somatic symptoms, psychiatric manifestations like sleep disruption, affective lability, and depressive syndromes can lead to disability, similar to other endocrine-withdrawal syndromes characterized by a feeling of impaired health after specific treatments.²⁵

GWS can be clinically severe and may occur despite apparently adequate replacement, so clinicians should not interpret persistent symptoms as undertreatment or recurrence. Moreover, symptoms often worsen during tapering to near physiologic doses, when psychiatric destabilization (insomnia, affective lability, anxiety, and depressive symptoms) can dominate patients' disability. Managing GWS is

even more challenging. An integrated endocrine and neuropsychiatric strategy should be pursued, aiming to maintain adequate glucocorticoid supplementation to prevent adrenal crises and to balance the risks and benefits of a short-term increase in glucocorticoids, a temporary hold, or a step-back in the taper scheme. The initial dose of glucocorticoids after surgery can be increased to 3- to 4-fold higher than the expected dose for replacement therapy to attenuate early symptoms of GWS. Additionally, if GWS symptoms occur during glucocorticoid treatment, a short trial with higher doses (avoiding late afternoon/night) can be performed to mitigate symptoms. However, a return to more physiological doses is expected to avoid delay in HPA-axis recovery. Larger morning doses and lower afternoon doses should be established as soon as possible, ideally within 4 to 6 weeks after surgery. The choice of glucocorticoid can be individualized. In a recent prospective

Table. Main Differences Between GWS and Adrenal Insufficiency After Curative Surgery for Endogenous Hypercortisolism

Features	GWS	Adrenal insufficiency
Mood and cognitive disturbances (affective lability, anxiety, depressive symptoms, "morning crash")	Common and often disproportionate	Can occur, usually less dominant
Hypersomnia	Common, can be prominent	Possible, but less typical
Orthostatic hypotension, presyncope	Uncommon	More suggestive, especially with triggers, such as physical or mental stressors; possible red flag for adrenal crisis
Hypoglycemia	Usually not detected	Possible
Anorexia	Possible	Common
Vomiting	Less typical	Red flag for adrenal crisis
Myalgias/arthralgias, pain syndromes	Very common	Common
Profound fatigue/low stress tolerance	Very common	Very common
Relationship to taper	Often worsens at near-physiologic dosing, but can occur also at supraphysiologic doses	Worsens with missed dosing or inadequate coverage
Objective evidence of inadequate cortisol reserve	Not required	Defining feature
Relationship to dose of glucocorticoid replacement	With supraphysiologic and physiologic doses	Worsens with missed dosing or inadequate physiologic coverage

study, once-daily prednisone was associated with greater improvement in early postoperative quality of life at 12 weeks, particularly in mental health–related domains and body pain, while the overall burden of withdrawal symptoms over time was comparable to that with hydrocortisone.²⁶ Proactive reassurance, involvement of family and caregivers, and targeted adjunctive supportive measures (nonsteroidal antiinflammatory drugs, rehabilitation, and early psychiatric interventions) should be considered.⁸

Clinical Case Vignettes

Case 1

A 54-year-old woman is evaluated for ACTH-independent Cushing syndrome due to a 3-cm lipid-poor adrenal adenoma associated with severe hypertension, diabetes, and fragility fractures. The patient reports a history of depression. After adrenalectomy, her hypertension and mood improve. She is discharged from the hospital on cortisone acetate, 25+12.5 mg daily (equivalent to 30 mg hydrocortisone). Six months postoperatively, she reports a 22-lb (10-kg) weight loss and a 4-in (10-cm) reduction in waist circumference. However, her psychiatric condition progressively worsens.

In addition to reevaluation by the psychiatrist, which of the following is the best next step?

- A. Proceed with glucocorticoid withdrawal to hasten HPA-axis recovery
- B. Maintain the replacement therapy and reevaluate shortly after
- C. Try a temporary increase in the glucocorticoid dosage
- D. Try a temporary increase in the glucocorticoid dosage and perform brain imaging
- E. Change to dexamethasone to relieve GWS

Answer: C) Try a temporary increase in the glucocorticoid dosage

A trial of increased doses of cortisone acetate was implemented (37.5+25+12.5 mg [equivalent to 60 mg hydrocortisone]), and psychiatric treatment was modified. She reported partial improvement in nocturnal symptoms (nighttime crying spells and intense despair), but persistence of “morning crash” and recurrent anxiety. A further improvement in psychiatric disorders was observed at the last follow-up (9 months, with no recovery of the HPA axis yet).

Case 2

A 52-year-old woman is diagnosed with ACTH-independent Cushing syndrome associated with abdominal obesity (waist circumference = 59 in [150 cm]; BMI = 42 kg/m²), resistant hypertension, concentric cardiac hypertrophy, impaired glucose tolerance, and fragility fractures. She undergoes left adrenalectomy followed by adrenal insufficiency treated with cortisone acetate, 25+12.5 mg (equivalent to 30 mg hydrocortisone), which is increased to 37.5+25 mg (equivalent to 50 mg hydrocortisone) due to fatigue, myalgia, and walking impairment, resulting in partial relief but persistent myalgia.

Which of the following is the best management of glucocorticoid therapy for this patient?

- A. Start tapering to physiologic doses of glucocorticoids
- B. Increase the glucocorticoid dosage to reduce myalgia
- C. Hold glucocorticoids until reassessment of the HPA axis
- D. Halve the dose to achieve a faster recovery of the HPA axis
- E. Change cortisone acetate to prednisone

Answer: A) Start tapering to physiologic doses of glucocorticoids

Cortisone acetate was reduced by 12.5 mg (equivalent to 10 mg hydrocortisone) at each step until reaching a dosage of 25+12.5 mg daily

(equivalent to 30 mg hydrocortisone). Clinical manifestations improved: waist circumference decreased to 43 in (109 cm) at 6 months and to 41 in (105 cm) at 12 months; weight decreased to 181 lb (82 kg) at 6 months, to 174 lb (79 kg) at 12 months, and to 183 lb (83 kg) at the last follow-up; and muscle strength improved, with the hand grip test increasing from 12.7 kg at 6 months to 23.3 kg 3 years after surgery. At the latest follow-up, 4 years after surgery, the HPA axis had not yet recovered.

Case 3

A 37-year-old woman is referred for an adrenal incidentaloma and MACS (cortisol after 1 mg dexamethasone-suppression test = 9.2 µg/dL [254 nmol/L]). She has ovarian cysts on estroprogestins, osteopenia, and fibromyalgia with joint pain, but no hypertension, diabetes, or fragility fractures. She undergoes left adrenalectomy with subsequent adrenal insufficiency. She is treated with cortisone acetate, 18.8+12.5 mg (equivalent to 25 mg hydrocortisone), then reduced to 12.5+6.25 mg (equivalent to 15 mg hydrocortisone). At 12 months, the morning cortisol concentration is 10 µg/dL (276 nmol/L). After cosyntropin stimulation, the cortisol concentration is 20.9 µg/dL (577 nmol/L). However, myalgia and joint pain have worsened.

Which of the following is the best next step?

- A. Withdraw glucocorticoids within a few days
- B. Withdraw glucocorticoids within a few weeks
- C. Consider reevaluation and potential interfering conditions
- D. Investigate worsening of rheumatological condition, while withdrawing glucocorticoids
- E. Temporarily increase the glucocorticoid dosage and reassess the patient

Answer: C) Consider reevaluation and potential interfering conditions

After careful reassessment, the patient reported taking estroprogestins after a consultation

with her primary care physician a few weeks earlier, despite previous advice to discontinue this treatment. Blood tests done when she was not on estroprogestins showed a morning cortisol concentration of 5 µg/dL (138 nmol/L). After 6 months, her cortisol concentration after cosyntropin stimulation was insufficient (13.1 µg/dL [361 nmol/L]). She reported persistence of myalgia and joint pain. At the last follow-up, 28 months after surgery, glucocorticoids were withdrawn after recovery of the HPA axis (cortisol after cosyntropin stimulation was 19.1 µg/dL [527 nmol/L]), without symptoms.

Key Learning Points

- Postoperative adrenal insufficiency is an expected physiologic consequence of remission of endogenous hypercortisolism; its duration depends on the etiology and preoperative severity, with adrenal etiologies often requiring the longest replacement.
- Assessment strategies vary, but decisions should prioritize patient safety while avoiding unnecessary prolonged replacement; dynamic testing can improve selectivity in MACS and reduce overtreatment.
- GWS is common after curing endogenous hypercortisolism, driving patients' disability, particularly through psychiatric decompensation, sleep disruption, and musculoskeletal symptoms, even at adequate replacement doses.
- Clinicians should explicitly manage the overlap state (adrenal insufficiency and GWS) by preventing acute crises, while using symptom-guided tapering, temporary stabilization, or step-back, when necessary, and providing early psychiatric and rehabilitative support.
- Counseling from physicians and support from family members and caregivers are key factors in improving the quality of life for individuals with GWS.

- Recovery should be monitored with appropriately timed testing (predose sampling and adequate washout after the last dose);

clinical judgment remains pivotal in the absence of well-established protocols in a complex clinical context.

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Metabolic Implications of Adrenal Incidentalomas: When Do We Intervene?

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the association of mild autonomous cortisol excess (MACS) with mortality and morbidity in patients presenting with an adrenal incidentaloma.
- Identify issues with biochemical assessment of adrenal incidentalomas.
- Differentiate among options for surgical intervention vs observation in patients with adrenal incidentalomas.

Significance of the Clinical Problem

Adrenal incidentalomas are frequently detected during abdominal cross-sectional imaging performed for reasons other than adrenal gland assessment. Most adrenal incidentalomas are benign adrenocortical adenomas. These adenomas are common, with prevalence increasing with age, and occur in up to 10% of people aged 80 years or older. Approximately 20% to 50% of adrenocortical adenomas secrete excess cortisol, as evidenced by a lack of serum cortisol suppression on an overnight dexamethasone-suppression test ($1.8 \mu\text{g/dL}$ [$>50 \text{ nmol/L}$]), independent of normal hypothalamic-pituitary regulation (termed

MACS),¹ but without classic features of Cushing syndrome. Thus, approximately 2% to 5% of people aged 70 to 80 years are living with cortisol excess. MACS is associated with a significantly increased risk of cardiometabolic morbidity and mortality,^{2,3} and mortality risk increases with higher postdexamethasone serum cortisol levels.⁴ Large population data suggest that this occurs above a postdexamethasone serum cortisol threshold of around $3 \mu\text{g/dL}$ (80 nmol/L).⁵⁻⁷

When several cortisol-related comorbidities are present, increasing evidence suggests that adrenal surgery may be justified in patients with established MACS, a suppressed plasma ACTH level, and a higher serum cortisol level after dexamethasone-suppression testing. Enthusiasm for investigation and intervention must be balanced against the patient's age, comorbidities, frailty assessment, and patient choice. Intervention for MACS is more likely to benefit patients aged 65 years or younger⁵ and those with hypertension.

Practice Gaps

- The best way to select patients who are appropriate candidates for surgical intervention is not yet fully established.
- It is not established how best to manage comorbidities when a conservative approach is adopted.

Discussion

Adrenal incidentalomas are common and often detected on imaging performed for reasons other than evaluating adrenal pathology. Although most are benign adrenocortical adenomas, incidentalomas may be unilateral or bilateral, and the differential is wide for both (*Box*). Two main questions should be addressed when a patient presents with an adrenal incidentaloma:

- Does imaging evaluation suggest the lesion is benign or malignant?
- Is the lesion hormonally active?

Box. Differential Diagnosis of Adrenal Incidentalomas

Unilateral adenomas	
Benign	Malignant
Adrenal cortex • Functioning adenoma • Nonfunctioning adenoma	• Adrenocortical cancer
Adrenal medulla • Pheochromocytoma (high signal on T2 MRI)	• Malignant pheochromocytoma
Others • Cyst • Myelolipoma • Ganglioneuroma • Hematoma	• Metastasis
Bilateral adenomas	
• Metastatic disease • Congenital adrenal hyperplasia • Lymphoma • Infection (tuberculosis, fungi, hydatid) • Hemorrhage • ACTH-dependent Cushing disease • Pheochromocytoma • Amyloidosis • Primary bilateral macronodular adrenal hyperplasia (PBMAH) • Bilateral adenoma	

Imaging Evaluation

Initial Imaging

- *Preferred modality:* Noncontrast CT is recommended as the first-line imaging modality for evaluating adrenal incidentalomas.
- *Benign criteria:* Lesions that are homogeneous with Hounsfield unit (HU) values ≤ 10 are considered benign, and no further imaging is required. If HU values are < 10 on a contrast-enhanced scan, it is not necessary to perform a noncontrast scan for further assessment. Large-scale data suggest that adrenal masses with HU values of 10 to 20 and a diameter of less than 4 cm are almost always benign.
- *Indeterminate lesions:* Lesions with HU values > 10 or heterogeneous appearance may require additional imaging or follow-up, usually in 6 to 12 months.

Additional Imaging

- *MRI with chemical shift:* May be useful for characterizing indeterminate lesions, particularly in patients with contraindications to CT (few). Loss of signal intensity on out-of-phase images suggests a benign adenoma.
- *FDG PET-CT:* Not routinely recommended but may be considered in patients with concern for malignancy, especially with a history of extra-adrenal malignancy, to assess for metastasis. It should be noted that benign lesions may be FDG PET-positive, so positivity is not cancer-specific.

Adrenal Biopsy

Adrenal biopsy may be considered in select cases when imaging is inconclusive and the results would change management, particularly in patients with known extra-adrenal malignancy.

Biochemical Assessment

Most patients with adrenal incidentalomas require biochemical evaluation, but in frail patients with poor performance status for whom intervention

other than treating comorbidities is not an option, avoiding biochemical evaluation may be reasonable. The one caveat is the assessment and management of adrenal insufficiency (see bilateral disease), if indicated, which should always be performed if this is a possibility.

Cortisol Secretion

1-mg Overnight dexamethasone-suppression test:

Recommended for all patients to assess for cortisol autonomy.

- **Serum cortisol $\leq 1.8 \mu\text{g/dL}$ ($\leq 50 \text{ nmol/L}$):**
Normal suppression
- **Serum cortisol $> 1.8 \mu\text{g/dL}$ ($> 50 \text{ nmol/L}$):**
Indicates MACS

Further evaluation: In patients with MACS, assess for comorbidities, including hypertension, type 2 diabetes, and osteoporosis, that may be related to cortisol excess.

Caveats for testing: The main risk is a false-positive serum cortisol result after dexamethasone, often in the range of 1.8 to 3 $\mu\text{g/dL}$ (50–80 nmol/L). An estimated glomerular filtration rate $< 60 \text{ mL/min per } 1.73 \text{ m}^2$ may be associated with a false-positive result.¹

Serum Dexamethasone Measurement

Serum dexamethasone measurement is not widely available. Dexamethasone measurement is recommended if the serum cortisol value during dexamethasone-suppression testing is suspected to be false-positive. A serum dexamethasone concentration $> 3.3 \text{ nmol/L}$ indicates sufficient dexamethasone levels.^{8,9}

Other Hormonal Assessments

- *Aldosterone-producing adenomas:* Evaluate plasma aldosterone concentration and plasma renin activity in patients with hypertension or hypokalaemia.
- *Sex steroid and steroid precursor profiling:* Consider in patients with imaging or clinical features suggestive of adrenocortical carcinoma, ideally using tandem mass spectrometry. If available, urinary steroid metabolomics may also help characterize indeterminate lesions.¹⁰ 17-Hydroxyprogesterone should be measured in patients with bilateral benign lesions that resemble hyperplasia to exclude classic congenital adrenal hyperplasia.

Management Strategies

Unilateral Adrenal Incidentalomas

- *Nonfunctioning, benign lesions:* No further imaging or hormonal evaluation is necessary.
- *MACS with comorbidities:* Consider surgical intervention in patients with MACS and suppressed basal plasma ACTH, taking into account patient age, general health, and preferences. Alternatively, and more often, management of comorbidities should follow standard care. Increasing data now show that adrenal surgery in appropriately selected patients improves cortisol-related comorbidities,¹¹ especially hypertension.¹² Adrenal insufficiency occurs in up to 50% of patients with MACS undergoing unilateral adrenal surgery.¹³ Limited data suggest that medical management directed at normalizing serum cortisol improves hypertension, but these are noncontrolled, anecdotal data, and prospective, large-trial data are needed.¹⁴
- *Indeterminate lesions:* Management should be individualized, often through multidisciplinary team discussions. Options include additional imaging, interval follow-up, or surgical resection, based on lesion characteristics and patient factors, such as a larger heterogeneous lesion in a young patient.

Bilateral Adrenal Incidentalomas

- **Classification:**
 - Primary bilateral macronodular adrenal hyperplasia
 - Bilateral adenomas
 - Morphologically similar but non-adenoma-like masses
 - Morphologically different masses
 - Hyperplasia (eg, congenital adrenal hyperplasia)
- **Evaluation:** Assess for cortisol autonomy and potential adrenal insufficiency, depending on the clinical scenario; infiltrative, metastatic disease, and hemorrhage can cause adrenal insufficiency.
- **Management:** Individualized based on hormonal activity, lesion characteristics, and patient comorbidities. Bilateral adrenalectomy is not recommended in the absence of overt Cushing syndrome.¹

Surgical Indications

- **Suspicion of malignancy:** Surgical resection by an expert high-volume surgeon is recommended for lesions with imaging features suggestive of adrenocortical carcinoma.
- **Functioning tumors:** Surgery is indicated for hormonally active tumors causing clinical syndromes.
- **Indeterminate lesions:** Consider surgery in younger patients (<40 years), pregnant women, or when lesions exhibit growth or change in imaging characteristics over time.
- **Surgical approach:** Procedures should be performed by experienced surgeons in high-volume centers. Minimally invasive techniques are preferred when appropriate.

Monitoring and Follow-Up

Nonoperative Management

- **Benign, nonfunctioning lesions:** No routine follow-up imaging or hormonal testing is required unless new clinical signs develop.
- **Indeterminate lesions not resected:** Repeat imaging (noncontrast CT or MRI) at 6 to 12 months to assess for changes in size or appearance.
- **MACS without surgery:** Annual clinical assessment for the development or progression of comorbidities related to cortisol excess.

Postsurgical Follow-Up

- **Histopathological evaluation:** Essential for confirming the diagnosis and assessing for malignancy.
- **Hormonal assessment:** Monitor for adrenal insufficiency postoperatively, especially in patients with cortisol-secreting tumors.

Clinical Case Vignettes

Case 1

A 73-year-old oxygen-dependent man with end-stage lung fibrosis is admitted to the hospital with a chest infection. CT shows a 2.8-cm right adrenal mass with an attenuation of 46 HU after contrast. Usual performance status is 3. His blood pressure is 100/65 mm Hg. No other relevant history is obtained. Physical examination findings do not suggest a generalized syndrome.

Which of the following is the best next step?

- Chemical shift MRI
- Noncontrast CT
- Overnight dexamethasone-suppression test
- Plasma metanephrine measurement
- None of the above

Answer: E) None of the above

In this clinical scenario, evaluation will not alter management, as intervention is not possible. Care would follow standard lines.

Case 2

A 40-year-old woman with hypertension and type 2 diabetes undergoes CT after an accident. Imaging reveals a 2-cm, homogeneous right adrenal mass with an attenuation of -5 HU.

Laboratory test results:

Postdexamethasone serum cortisol = $5 \mu\text{g/dL}$

(SI: 138 nmol/L)

Basal plasma ACTH = 5 pg/mL (SI: 1.1 pmol/L)

Hemoglobin A_{1c} = 8.1% (65 mmol/mol)

On DXA, the lumbar spine T-score is -2.6 .

What further tests and management are indicated?

- Medical management of comorbidities only
- Plasma free metanephrine measurement; if elevated, refer for adrenal surgery
- Refer for adrenal surgery
- Check femoral neck bone mineral density; if low, consider adrenal surgery
- Repeat noncontrast CT in 6 to 12 months

Answer: C) Refer for adrenal surgery

An HU value less than 10 means that measuring plasma metanephrines is unnecessary. Cortisol excess affects the axial skeleton, and this patient already has osteoporosis. The HU value of -5 indicates that the lesion is benign, and no further imaging is needed. While medical management of comorbidities is an option, in someone of this age with a “full house” of likely cortisol-driven comorbidities, adrenal surgery would be more appropriate, with careful monitoring for potential adrenal insufficiency in the postoperative period, which may last 6 months or more.

Case 3

A 35-year-old woman with hypertension and diet-controlled type 2 diabetes undergoes CT for evaluation of abdominal pain, and imaging reveals a 3.5-cm right adrenal mass with an attenuation of -8 HU.

Laboratory test results:

Serum cortisol after 1 mg overnight dexamethasone-suppression test = $3.6 \mu\text{g/dL}$ (SI: 98 nmol/L)

Basal plasma ACTH (9 AM) = 22 pg/mL

(SI: 4.8 pmol/L)

Plasma aldosterone-to-renin ratio, normal

What further tests and management are indicated?

- Medical management of comorbidities only
- Plasma free metanephrine measurement; if elevated, refer for adrenal surgery
- Refer for adrenal surgery
- Measure bone mineral density and consider adrenal surgery
- Repeat noncontrast CT in 6 to 12 months

Answer: A) Medical management of comorbidities only

An HU value less than 10 indicates that measuring plasma metanephrines is unnecessary. This is a benign lesion, and no further imaging is needed. Because the morning basal plasma ACTH is not suppressed, full adrenal autonomy is not demonstrated, and adrenal surgery would not be indicated despite this patient's young age. Managing comorbidities is important, and it would be sensible to assess for progression of clinical or biochemical features of cortisol excess annually for several years. The decision regarding surgery may change if basal morning ACTH suppression is confirmed in the future.

Key Learning Points

- Adrenal incidentalomas causing MACS are common.
- MACS is associated with cardiometabolic morbidity and mortality, but the decision to

investigate should weigh imaging features and patient performance status.

- HU values less than 10 indicate benign lesions that do not require repeat imaging or evaluation for pheochromocytoma.
- Minimally invasive surgery by a high-volume adrenal surgeon should be considered for selected patients with multiple MACS-related comorbidities due to a unilateral adrenal

adenoma and suppressed basal morning plasma ACTH, with the goals of identifying and managing adrenal insufficiency.

- In the context of bilateral disease, bilateral adrenal surgery is not recommended for MACS.
- Large-scale, prospective controlled trials are needed to assess medical approaches to managing MACS.

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Challenges in the Diagnosis and Management of Adrenal Insufficiency

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Select a test to diagnose adrenal insufficiency (AI).
- Differentiate among the causes of AI.
- Prevent and treat adrenal crisis.
- Establish cortisol replacement therapy for a patient with AI.

Significance of the Clinical Problem

AI results from a deficiency of cortisol, the essential stress hormone secreted by the adrenal glands. When untreated, AI results in death due to adrenal crisis.¹ The causes of AI are classified according to which component of the hypothalamic-pituitary-adrenal (HPA) axis is disrupted. Adrenal disorders are described as *primary AI*, pituitary disorders are described as *secondary AI*, and hypothalamic disorders are described as *tertiary AI*. In childhood, congenital adrenal hyperplasia (CAH) is the most common cause of primary AI, while autoimmune disease is the most common cause of acquired primary AI. In adults, secondary AI is more common than primary AI and is most often caused by

benign pituitary adenomas. Worldwide, adults and children are at risk of AI caused by infectious diseases; however, in most countries, the most common cause is iatrogenic adrenal suppression from the use of anti-inflammatory glucocorticoids (steroid medication). It is estimated that 1% to 3% of the population is prescribed systemic steroids,² and approximately 50% of these individuals have suppressed adrenal function.³ Adrenal crisis and death also occur in patients on other steroid formulations,⁴ and approximately 20% of adults and 40% of children with asthma treated with high-dosage inhaled steroids have AI.⁵ Drugs such as opioids and immune checkpoint inhibitors also cause AI. The frequency of testing for AI is increasing due to the large numbers of patients on steroid and opioid medications and heightened awareness of AI in these patient groups.

Practice Gaps

- Several tests can be used to diagnose AI. It is important to select the right test to avoid false-positive and false-negative results. Having knowledge of which test to use when and on whom is essential in making the correct diagnosis.
- Determining the cause of AI is important. The most common cause, glucocorticoid-induced

AI, is often missed because clinicians have not checked for glucocorticoid use.

- Adrenal crisis remains the most common cause of death in patients with AI because health care workers and patients are not adequately educated on how to treat and prevent this life-threatening condition.
- Several treatment regimens are available for AI, but knowledge is limited about which regimen is the best.

Discussion

Symptoms of AI are nonspecific and include fatigue, resulting in a large testing burden despite the fact that most patients who are tested have normal adrenal function. When undiagnosed, AI risks adrenal crisis, with life-threatening cardiovascular collapse and a mortality rate of approximately 6%.⁶ Annually, 6% to 8% of individuals with AI experience a crisis. Delayed diagnosis is common, so it is important to have a rapid screening test for AI.⁷ Adrenal crisis requires immediate treatment. In a large, prospective study, 8.3 episodes of adrenal crisis per 100 patient-years were reported, with an associated mortality rate of 0.5 per 100 patient-years.⁸ Patients with CAH, on average, use sick-day rules 171 times during their life and attend the hospital for an adrenal crisis 11 times.⁹ Patient education is essential regarding adrenal crisis precipitants, the need to increase glucocorticoid doses during periods of stress, and the importance of recognizing the early features of adrenal crisis.

Treatment of AI involves replacing cortisol, which can be achieved with several regimens. Hydrocortisone and cortisone are widely recommended as first-line glucocorticoids in clinical guidelines because they are less potent than synthetic glucocorticoids and may be associated with fewer adverse effects.¹⁰ Doses can be titrated in small increments, and treatment effectiveness can be assessed clinically. The use of synthetic glucocorticoids (prednisolone and prednisone) is recommended to be restricted to patients in whom symptoms of cortisol deficiency are not adequately controlled with hydrocortisone or cortisone, or

when adherence to a multiple daily dose regimen is poor. The use of dexamethasone is discouraged because of the risk of excess glucocorticoid exposure. Modified-release hydrocortisone formulations are available in the United Kingdom and Europe: Plenadren (Takeda Pharmaceutical Company Limited), a once-daily formulation that replaces daytime cortisol levels, and Efmody (Neurocrine Biosciences), a twice-daily formulation that replaces the early-morning rise in cortisol and daytime cortisol levels in patients with CAH.

Clinical Case Vignettes

Case 1

A 25-year-old woman with no relevant medical history and taking no medications presents to your afternoon clinic with concerns of fatigue and weight loss. There are no signs of AI, but you decide it is important to exclude this diagnosis.

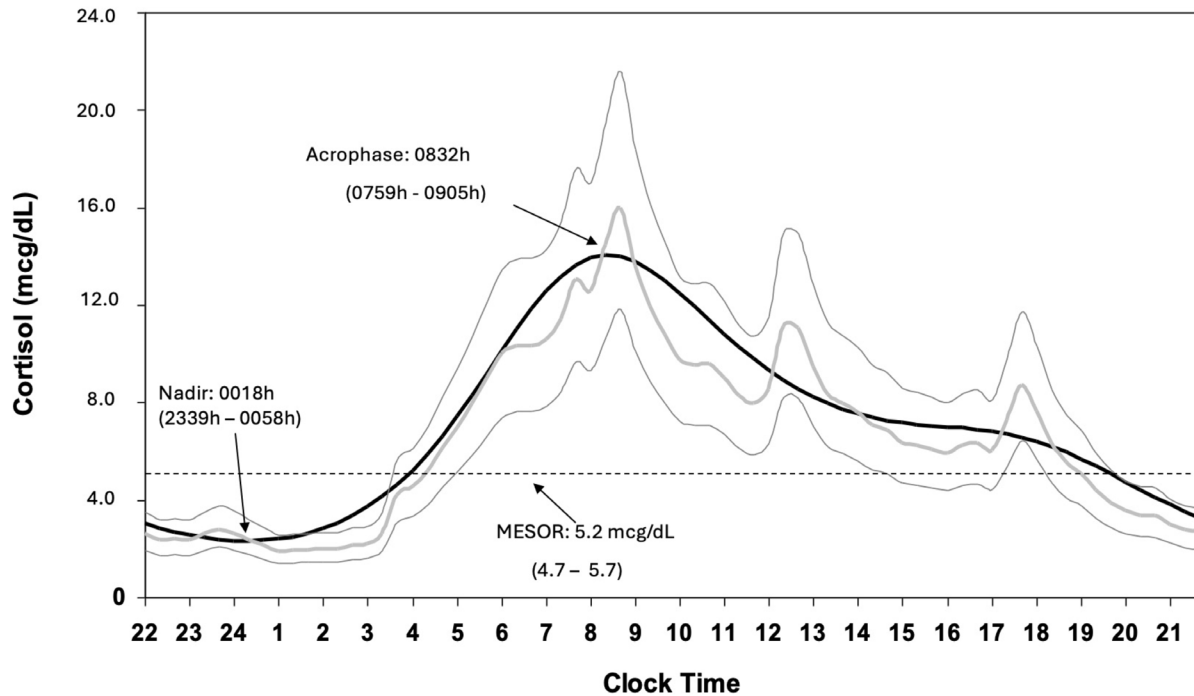
Which of the following tests is most likely to give a false-positive result?

- Cosyntropin-stimulation test
- Serum cortisol measured in a sample drawn in the clinic
- Waking salivary cortisone measurement
- Early-morning measurement of serum cortisol and ACTH
- Early-morning measurement of serum cortisol

Answer: B) Serum cortisol measured in a sample drawn in the clinic

Cortisol has a circadian rhythm with high levels in the morning and low levels in the afternoon and evening (*Figure 1, following page*). Waking cortisol levels vary among healthy individuals, with a mean peak waking cortisol concentration of 15 µg/dL (414 nmol/L).¹¹ A morning cortisol value less than 5 µg/dL (<140 nmol/L) is considered to reflect relative AI.¹⁰ Afternoon and evening cortisol levels often fall below 5 µg/dL (<140 nmol/L). Early-morning cortisol measurement, with or without ACTH measurement, and waking salivary cortisone measurement are all good screening tests for AI.

Figure 1. Physiological Cortisol Circadian Rhythm



The figure shows the geometric mean ± 2 SD of serum cortisol concentration, calculated from 20-minute sampling over a 24-hour period, in 33 healthy participants. The fitted cosinor (—) is the average of harmonic regressions that were a fit for the individual subject data. Cortisol has a distinct circadian rhythm, with a peak of 15.5 $\mu\text{g/dL}$ (95% CI, 11.7–20.6 $\mu\text{g/dL}$) at 0832h and a nadir of less than 2.0 $\mu\text{g/dL}$ (95% CI, 1.5–2.5 $\mu\text{g/dL}$) at 0018h. Mesor = midline estimating statistic of rhythm. Acrophase = time of peak using a 24-hour clock with midnight taken as origin. Nadir = time of trough cortisol level. The mean and 95% CI are shown for the mesor, acrophase, and nadir. Reprinted from Debono M, Ghobadi C, Rostami-Hodjegan A, et al. Modified-release hydrocortisone to provide circadian cortisol profiles. *J Clin Endocrinol Metab.* 2009;94(5):1548–1554.¹¹

Case 1, Continued

The patient then tells you she is on an oral contraceptive.

Which of the following tests would be the best to exclude AI?

- A. Cosyntropin-stimulation test
- B. Serum cortisol measured in a sample drawn in the clinic
- C. Waking salivary cortisone measurement
- D. Early-morning measurement of serum cortisol and ACTH
- E. Early-morning measurement of serum cortisol

Answer: C) Waking salivary cortisone measurement

Oral contraceptives increase corticosteroid-binding globulin and therefore result in spuriously high cortisol values both in the morning and

after cosyntropin stimulation. When assessing the HPA axis in women on oral estrogens, it is common practice to discontinue the estrogen for 6 weeks before conducting the test. However, this approach risks delayed diagnosis and unintended pregnancy. Salivary cortisone reflects free serum cortisol levels, as free serum cortisol is rapidly converted to cortisone in the salivary gland. Salivary cortisone better reflects serum cortisol levels than salivary cortisol,¹² and oral hydrocortisone does not interfere with its measurement. Salivary cortisone can be measured when serum cortisol levels are low.¹³ Salivary steroids are stable at room temperature. Thus, samples can be collected at a patient's home and mailed to the laboratory.¹⁴ Waking salivary cortisone collected at home has been shown to be as accurate as cosyntropin-stimulation testing in diagnosing AI.⁷

Case 2

A 70-year-old man in the orthopedic ward has a low sodium concentration and a clinical picture consistent with syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Measurement of which of the following analytes would best exclude an endocrine cause?

- A. Aldosterone
- B. Free T₄
- C. Free T₃
- D. Cortisol
- E. ACTH

Answer: D) Cortisol

AI can present with a clinical picture of SIADH, with a low sodium concentration. Primary AI usually presents with low sodium and high potassium values, but this is not always the case. Patients with AI (treated with replacement therapy) who become stressed and have not increased their hydrocortisone dose present with a clinical picture consistent with SIADH. Primary hypothyroidism can present with AI, and TSH should be measured, but not free T₄ or T₃, as these might be low due to sick euthyroid syndrome. ACTH concentrations may be elevated in acutely unwell patients, but this does not reflect the HPA axis response to sickness. Aldosterone levels are low or suppressed in the setting of SIADH.

Case 2, Continued

The cortisol level comes back as undetectable.

Measurement of which of the following analytes would best differentiate the cause?

- A. Aldosterone
- B. Free T₄
- C. Free T₃
- D. Free cortisol
- E. ACTH

Answer: E) ACTH

When AI is diagnosed, the first step is to determine whether it is primary or secondary, as this will guide further investigation. It is important to draw the cortisol sample at the same time as the ACTH sample, so they are paired. A high ACTH concentration in the presence of low or undetectable cortisol is diagnostic of primary AI, and an ACTH concentration that is in reference range, low, or undetectable in the presence of low cortisol suggests either secondary or tertiary AI.

Case 2, Continued

The patient had undergone spinal surgery 48 hours before the referral. Laboratory results have documented undetectable cortisol and ACTH. You check the records and see that the patient had received 8 mg of dexamethasone with their premedication. You had already prescribed the patient hydrocortisone when you received the result of undetectable cortisol.

Which of the following is the best next step?

- A. Continue hydrocortisone until the patient recovers from surgery
- B. Stop hydrocortisone in the evening and measure next-morning cortisol
- C. Stop treatment of SIADH
- D. Start prednisolone
- E. Continue dexamethasone

Answer: B) Stop hydrocortisone in the evening and measure next-morning cortisol

Glucocorticoid-induced AI should be considered in any patient presenting with low cortisol, as this is the most common cause of AI through HPA-axis suppression.¹⁵ It is important to ask the patient and their doctor about glucocorticoid use and to review the prescription history to determine whether the patient has received any inhaled, oral, transdermal, and/or parenteral glucocorticoid. This can often be missed, especially if given with premedication, as in this patient's case. Adrenal suppression has not been reported with glucocorticoid treatment of less than 3

weeks' duration, so this patient's HPA axis can be tested 72 hours after parenteral dexamethasone. If hydrocortisone is stopped, it will be cleared within 12 hours. In patients who have received glucocorticoids for longer than 3 to 4 weeks, the guidelines suggest the following:

- (1) Recovery of the HPA axis is indicated if the cortisol concentration is greater than 10 $\mu\text{g/dL}$ ($>300 \text{ nmol/L}$) and glucocorticoids can be stopped safely
- (2) If the cortisol concentration is between 5 and 10 $\mu\text{g/dL}$ (150–300 nmol/L), the physiologic glucocorticoid dose should be continued, and morning cortisol measurement should be repeated after an appropriate period (usually weeks to months)
- (3) If the cortisol concentration is less than 5 $\mu\text{g/dL}$ ($<150 \text{ nmol/L}$), the physiologic glucocorticoid dose should be continued, and the morning cortisol measurement should be repeated after a few months¹⁵

Case 3

A 17-year-old woman presents to the emergency department with diarrhea and vomiting. She has a slight fever and is hypotensive. She has a history of primary hypothyroidism and is on levothyroxine, 75 mcg daily. She is dehydrated, her blood glucose concentration is normal, her sodium concentration is low, and her potassium concentration is high.

Which of the following is the best action to take now?

- A. Draw blood for cortisol measurement and ask the laboratory to process it urgently
- B. Draw blood for cortisol measurement and immediately administer hydrocortisone, 100 mg intravenously
- C. Draw blood for free T_4 measurement and increase the levothyroxine dosage to 100 mcg daily
- D. Immediately start a 5% dextrose infusion to rehydrate
- E. Start an insulin infusion

Answer: B) Draw blood for cortisol measurement and immediately administer hydrocortisone, 100 mg intravenously

This patient has all the symptoms and signs of an adrenal crisis and therefore needs immediate treatment. Blood should be drawn and sent to the lab with a request to store the ACTH sample, so this analyte can be measured if AI is diagnosed. Hydrocortisone should be administered intravenously or intramuscularly and can be continued or switched to an infusion. The guidelines recommend that patients with suspected adrenal crisis should be treated with an immediate parenteral injection of hydrocortisone, 100 mg (50 mg/m² for children), followed by appropriate fluid resuscitation and 200 mg (50–100 mg/m² for children) of hydrocortisone per 24 hours (via continuous intravenous therapy or injection every 6 hours). Age- and body surface-appropriate dosing is required in children.¹⁰

Case 3, Continued

The patient's cortisol concentration before treatment is documented to be 2.7 $\mu\text{g/dL}$ (75 nmol/L), and her ACTH concentration is greatly elevated, thus confirming the diagnosis of adrenal crisis. The patient makes an uneventful recovery over 48 hours on intravenous hydrocortisone. Her regimen is converted to oral hydrocortisone 3 times daily, and fludrocortisone is started.

Before hospital discharge, which of the following is essential?

- A. Wean her to a replacement dose of hydrocortisone
- B. Measure ACTH to ensure it has normalized
- C. Reassess thyroid function
- D. Teach her about stress dosing and the sick-day rules
- E. Measure renin

Answer: D) Teach her about stress dosing and the sick-day rules

The most common cause of death in patients with established AI is adrenal crisis, and it is therefore essential that the patient receives information about stress dosing and sick-day rules and is given an emergency pack before leaving the hospital. All the other actions can be done after hospital discharge. The guidelines recommend the following:

- (1) For the prevention of adrenal crisis, adjust the glucocorticoid dose according to the severity of illness or the magnitude of the stressor
- (2) Patient education should include glucocorticoid adjustments in stressful events and adrenal crisis prevention strategies, including parenteral self- or lay-administration of emergency glucocorticoids
- (3) All patients should be equipped with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat adrenal crisis and the need for immediate parenteral steroid treatment in the event of an emergency
- (4) Every patient should be equipped with a glucocorticoid injection kit for emergency use and be educated on how to use it¹⁰

Case 3, Continued

At an outpatient visit 6 months after diagnosis, the patient states she has been well, but she feels fatigued in the morning. Her laboratory results are all satisfactory, including free T₄ and renin measurements, as well as a cortisol day curve. She has no clinical or biochemical evidence of other autoimmune disorders, such as celiac disease.

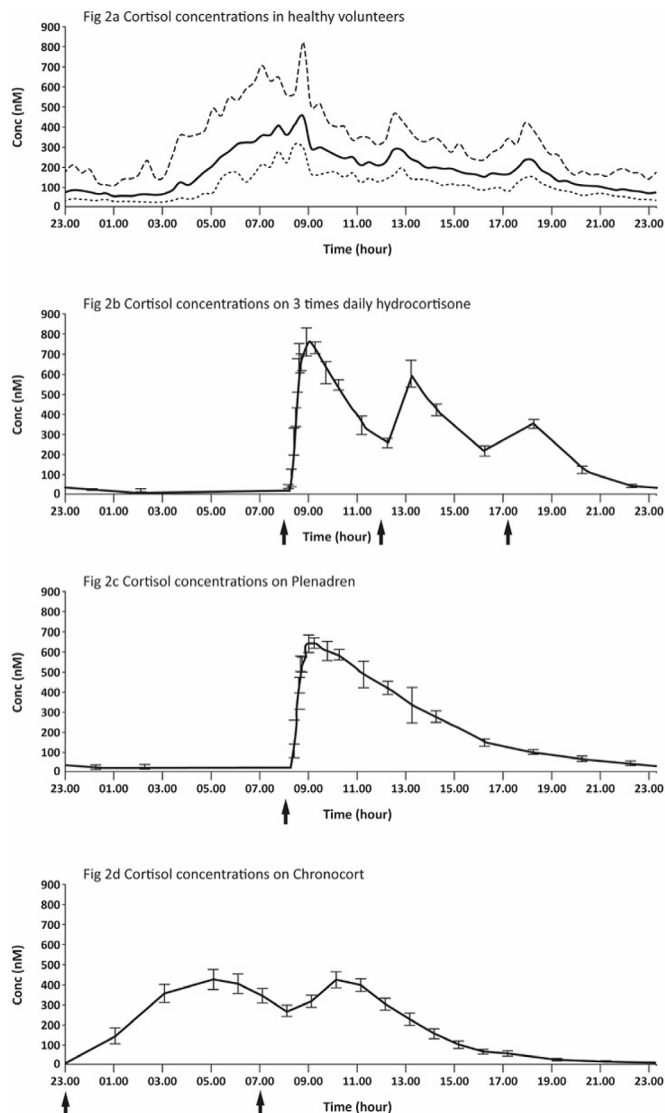
Which of the following might improve her fatigue?

- A. Increase the hydrocortisone dose over the day
- B. Increase the fludrocortisone dose
- C. Change the treatment regimen
- D. Take the hydrocortisone dose last thing at bedtime
- E. Change treatment to dexamethasone

Answer: C) Change the treatment regimen

Fatigue is common among patients with AI on replacement therapy, regardless of the regimen used. However, evidence suggests that some treatment regimens improve quality of life and reduce fatigue. Patients often think that increasing the hydrocortisone dose will help; however, the evidence suggests that higher doses do not improve quality of life or reduce fatigue.¹⁶ There is no evidence that increasing the fludrocortisone dose helps if the renin level is normal. Taking hydrocortisone at night might negatively affect sleep and will be cleared from the circulation before waking. Dexamethasone is contraindicated, as it is difficult to titrate, has no mineralocorticoid action, and has an increased adverse effect profile. Hydrocortisone is given twice or thrice daily, but no blinded study has compared these regimens. Most clinicians recommend taking the first dose first thing in the morning to combat morning fatigue. In open-label studies, continuous subcutaneous hydrocortisone infusion has been shown to improve quality of life. A double-blind study of hydrocortisone replacement in 10 patients with primary AI using a continuous subcutaneous infusion found no effect on quality of life.¹⁷ However, the patient number was small, and the patients had a good quality of life at baseline. There are 2 modified-release hydrocortisone formulations available in the United Kingdom and Europe. Plenadren (Takeda Pharmaceutical Company Limited) is a once-daily formulation that replaces daytime cortisol levels, and Efmody (Neurocrine Biosciences) is a twice-daily formulation that replaces the early-morning rise in cortisol, as well as daytime cortisol levels, in patients with CAH (*Figure 2, following page*).¹⁸⁻²² In open-label studies, Plenadren improves quality of life.²³ Efmody improves disease control in patients with CAH,¹⁹ and in a randomized, double-blind study, Efmody improved quality of life and reduced fatigue in patients with primary AI.²⁴

Figure 2. Cortisol Concentrations in Healthy Volunteers and in Patients Treated With Hydrocortisone and Modified-Release Hydrocortisone Formulations



Panel (a), Cortisol concentrations measured by liquid chromatography–tandem mass spectrometry in healthy volunteers (mean, 10th and 90th percentile).²⁰ Panel (b), Cortisol concentrations measured by immunoassay on 3 times daily immediate-release hydrocortisone, 20 to 40 mg, in patients with adrenal insufficiency (mean and 95% CI).²¹ Panel (c), Cortisol concentrations measured by immunoassay on once-daily Plenadren, 20 to 40 mg, in patients with adrenal insufficiency (mean and 95% CI).²¹ Panel (d), Cortisol concentrations measured by liquid chromatography–tandem mass spectrometry on twice-daily Chronocort with 20 mg at 2300h and 10 mg at 0700h in patients with CAH (mean and standard error of the mean).²² Arrows on the x-axis represent the timing of dosing.¹⁸

Key Learning Points

- When screening for AI, it is important to recognize the circadian rhythm of cortisol: it rises overnight, peaks on waking, and then declines during the day. A random cortisol measurement from an afternoon sample may be low, leading to a false-positive result. An early-morning serum cortisol measurement or, where available, a waking salivary cortisone measurement, is a good screening test for AI, and a cosyntropin-stimulation test can be done at any time to confirm a diagnosis if the screening test is borderline. Importantly, some drugs interfere with cortisol results, specifically oral estrogens, which raise corticosteroid-binding globulin and lead to spuriously high serum cortisol levels. Waking salivary cortisone is a good test when screening women on oral contraceptive pills. Waking salivary cortisone is a better screening test than waking salivary cortisol because free serum cortisol is converted to salivary cortisone.
- Diagnosing the cause of AI, which may be primary (adrenal), secondary (pituitary), or tertiary (hypothalamic), is important. ACTH is the first analyte to measure if a low cortisol value is documented. This should be a paired sample with cortisol. A high ACTH concentration in the presence of a low cortisol concentration suggests the patient has primary adrenal AI, such as Addison disease. A low or undetectable ACTH concentration paired with a low cortisol concentration suggests secondary or tertiary AI. The most common cause of tertiary AI is glucocorticoid-induced AI. When reviewing a patient with AI, it is important to ask about anti-inflammatory glucocorticoid therapy, such as inhalers, creams, oral medications, and injections (including intra-articular).
- Immediate treatment is required for adrenal crisis, and adrenal crisis remains the most common cause of death in patients with AI. All patients with an AI diagnosis should be given

an emergency pack and taught the importance of stress dosing and sick-day rules.

- Quality of life is impaired in some patients with AI, and the most common symptom is fatigue. In a patient with AI on stable replacement therapy, other causes of fatigue should be excluded, especially autoimmune disorders in patients with primary AI. Once

other causes of fatigue are excluded, the treatment regimen should be considered. There is no evidence that increasing the overall dose of hydrocortisone improves quality of life. However, emerging evidence suggests that replacing the early-morning cortisol rise reduces fatigue and improves health-related quality of life.

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BONE AND MINERAL METABOLISM

Beyond Basic Dual-Energy X-Ray Absorptiometry

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Manage patients at risk of fractures by using the trabecular bone score (TBS) to refine 10-year fracture risk estimates.
- Explain what full femur imaging (FFI) is used for and when to use it for detecting incomplete atypical femoral fractures (AFFs).
- Illustrate how total body composition scans with dual-energy X-ray absorptiometry (DXA) can be used for patients with sarcopenia.

Significance of the Clinical Problem

DXA has been used in clinical practice for nearly 40 years. Hip and spine scans for bone mineral density (BMD) have been the standard-of-care measurements for assessing skeletal health. Recent developments in DXA scanning include: (a) TBS of the spine to refine fracture risk assessment in FRAX, (b) FFI for detecting incomplete AFFs, and (c) total body composition scans to measure lean and fat mass, which can be useful for diagnosing sarcopenia. This chapter illustrates how these tools are used in patient care.

Practice Gaps

- TBS has been recommended in multiple guidelines (International Society for Clinical Densitometry [ISCD], International Osteoporosis Foundation [IOF], European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis [ESCEO]) to refine fracture risk assessment, but few clinicians outside the bone health community are aware of this tool.
- FFI has been used to detect incomplete AFFs. AFFs are stress fractures; incomplete AFFs are often present before complete AFFs, which require urgent surgical fixation. More frequent use of FFI may help detect AFFs earlier and prevent their progression to complete AFFs.
- Total body composition scans are useful for assessing fat and lean mass. Currently, coverage for these scans varies. They can be helpful in diagnosing sarcopenia or assisting in decision-making regarding weight-loss regimens.

Discussion

Trabecular Bone Score

TBS is an advanced, noninvasive software tool applied to standard lumbar spine DXA to evaluate bone microarchitecture and quality. By measuring textural variations in the image, TBS predicts fracture risk independently of BMD and can identify patients with low fracture risk despite low BMD or high fracture risk despite normal BMD. TBS enhances fracture risk prediction and

helps diagnose bone fragility in patients with certain medical conditions, such as diabetes, where BMD alone may not indicate high risk. It can also be used to monitor structural improvements in response to bone formation therapies.

Full Femur Imaging

FFI is a specialized, low-dose imaging technique that captures the entire femur, not just the hip joint, to detect radiographic abnormalities across the spectrum of AFFs. Abnormalities include focal thickening of the lateral cortex on the periosteal or endosteal side, a lucency that corresponds to a fracture line, and beaking (focal thickening plus lucent line or “dreaded black line”). It is often used for patients on long-term potent antiresorptive therapies, especially those on glucocorticoid therapy. FFI can be performed on GE Lunar and Hologic densitometers as part of a routine BMD assessment. Early detection of incomplete AFFs can enable appropriate intervention to prevent a complete fracture.

Total Body Composition

Total body composition is a highly accurate, noninvasive imaging test that measures body fat and lean muscle mass. Using low-dose X-rays, total body composition provides a comprehensive report detailing body fat percentage, regional fat distribution (including visceral fat vs subcutaneous fat), and muscle symmetry. The test can often be done within 10 minutes. Athletes commonly use total body composition to refine their nutrition and training to enhance performance. It is also used to diagnose and monitor sarcopenia. Additionally, it can help individuals track weight loss and assess whether they are losing fat rather than muscle.

Clinical Case Vignettes

Case 1

A 72-year-old White postmenopausal woman presents with a history of wrist fracture 15 years ago when she was pulled by a dog and fell on her

outstretched hand. She is otherwise well and is physically active without increased fall risk. She has taken vitamin D supplements (25 mcg [1000 international units] daily) for the past 15 years and has never taken any bone medications.

Her physical examination findings are unremarkable, with normal wall-to-occiput distance and rib-pelvic span. There is no percussion tenderness over the spine, and she has a normal tandem gait.

On DXA today, her lumbar spine (L1-L4) T-score is -0.3 , left femoral neck T-score is -1.7 , and left total hip T-score is -1.6 . According to FRAX, based on her age, sex, and BMD T-score, her 10-year major osteoporotic fracture risk is 15%, and her 10-year hip fracture risk is 2.7%.

Which of the following assessments would be most helpful with decision-making regarding this patient’s treatment?

- A. Height and weight
- B. TBS
- C. Distal radius BMD
- D. Urinary calcium excretion
- E. Length of the radius

Answer: B) TBS

TBS, a surrogate measure of bone quality and microarchitecture, can help refine this patient’s fracture risk assessment. Bone strength depends on bone density, bone quality, and bone structure; bone density is not the sole determinant of fracture risk.¹ While BMD measured by DXA accounts for approximately 60% to 70% of the variation in bone strength, the remaining 30% to 40% is determined by factors that contribute to the structural integrity and material properties of the bone. TBS quantifies the grey level of pixels, estimates the homogeneity or heterogeneity of the projected image, and is an independent risk factor for fractures.²

TBS can be measured using the patient’s lumbar spine DXA scan. It is FDA approved and incorporated into the DXA software. Government approval varies depending on your country of

residence. A high TBS value (>1.350) correlates with strong, fracture-resistant microarchitecture, whereas a low TBS value (<1.200) correlates with weak, fracture-prone microarchitecture.

TBS can be incorporated into FRAX to refine fracture risk assessment. In this vignette, the effects of different TBS values on fracture risk are shown in the *Table*.

According to ISCD guidelines, in individuals for whom you are trying to decide whether to treat with bone medications, TBS can provide a refined fracture risk assessment and help with clinical decision-making.^{3,4}

Case 2

A 69-year-old Asian postmenopausal woman presents with a history of rheumatoid arthritis (never on biologic agents) and osteoporosis. She has never had a fracture. She has been taking oral alendronate, 70 mg weekly, for the past 10 years. Five years ago, another endocrinologist recommended teriparatide, a bone-formation therapy, but she could not tolerate it and discontinued after less than 1 month due to severe arthralgias and myalgias. In addition to alendronate, her current medications and supplements include methotrexate, 7.5 mg weekly, and vitamin D, 50 mcg (2000 international units) daily. She has adequate dietary calcium intake (~ 1200 mg daily).

Recent DXA shows a lumbar spine (L1-L4) T-score of -3.3 , a left femoral neck T-score of -3.1 , and a left total hip T-score of -2.8 . Compared with a BMD scan performed 18 months ago, her lumbar spine BMD has decreased by 5%, while her femoral neck and total hip BMD have remained stable.

Based on her age, sex, and BMD T-score, her 10-year absolute major osteoporotic fracture risk is 20%, and her hip fracture risk is 4.3% (calculated using FRAX).

Which of the following assessments would be most helpful with treatment recommendations?

- A. Serum calcium measurement
- B. No other assessments are needed
- C. FFI by DXA or full femur X-ray
- D. Distal radius BMD
- E. Height and weight

Answer: C) FFI by DXA or full femur X-ray

This woman has many risk factors for fractures: rheumatoid arthritis, very low BMD, menopause, etc. Indeed, based on her FRAX scores, she is at high risk for fractures. According to the 2020 Endocrine Society Guidelines for the Management of Osteoporosis in Postmenopausal Women, she should continue her current therapy without a drug holiday or switch to another osteoporosis treatment.⁵ However, long-term bisphosphonate therapy without a drug holiday can increase the risk of rare adverse effects such as AFFs, especially in Asian women and in the setting of rheumatoid arthritis.⁶

FFI can help identify incomplete AFFs or changes in the AFF spectrum. This type of imaging can be done at the same time as a routine DXA. Current ISCD guidelines suggest performing FFI at the time of DXA for individuals who have been on potent antiresorptive therapy for 3 or more years.⁷ A negative scan can provide reassurance for continuing current bisphosphonate therapy

Table. Patient's Fracture Risk Assessment With and Without TBS Adjustment

TBS	10-Year absolute major osteoporotic fracture risk by FRAX	10-Year absolute hip fracture risk by FRAX
Without TBS adjustment	15%	2.7%
With TBS adjustment		
TBS = 1.350	14%	2.5%
TBS = 0.930	23%	4.3%

or switching to a bone formation agent such as romosozumab. Potent bisphosphonate therapies, denosumab, and romosozumab have been associated with AFFs.

Case 3

A 65-year-old Hispanic postmenopausal woman presents for management of type 2 diabetes and class II obesity. She has been on metformin, 500 mg 3 times daily, and sitagliptin, 100 mg daily, for the past 5 years. Despite lifestyle modifications, including exercise and dietary changes, her weight is unchanged and her hemoglobin A_{1c} level remains elevated at 8.7% (72 mmol/mol). She also has bilateral knee osteoarthritis and feels that she has been losing leg muscle mass after menopause. She is otherwise healthy but leads a sedentary lifestyle due to her occupation. She is interested in trying a GLP-1 receptor agonist for weight loss and improved glycemic control, but she is concerned about muscle loss. She is wondering if there are tests available to determine whether she has sarcopenia.

Which of the following assessments would you recommend?

- A. 6-Minute walk test
- B. Hip and spine BMD
- C. Height and weight
- D. Albumin measurement
- E. Total body composition

Answer: E) Total body composition

Sarcopenia is the loss of muscle mass, strength, and function that occurs with aging. It is a major risk factor for poor prognosis, contributing to falls, fractures, and physical disabilities, as well as increasing the risk of cardiovascular disease, cancer, and mortality.⁸ Sarcopenic obesity is associated with higher mortality in older adults.⁹ Menopause, physical inactivity, obesity, weight loss, certain medications, and chronic medical conditions are risk factors for sarcopenia. While weight loss can benefit individuals with diabetes and obesity by improving glycemic control,

reducing cardiovascular risk, and slowing the progression of osteoarthritis, adverse effects often include loss of muscle and bone mass. Thus, engaging in weight-bearing and resistance exercises and ensuring a high protein intake are important to counteract muscle and bone loss during weight loss.

For this patient, the SARC-F can be used as a screening questionnaire for sarcopenia.¹⁰ If positive, muscle strength can be measured by a hand-grip dynamometer (<27 kg for men, <16 kg for women) or a 5-time chair test (>15 s).¹¹ If positive, muscle mass can be measured with total body DXA. Total body composition scans using DXA can provide measurements of lean and fat mass and are often used by elite athletes to monitor training progress. For the diagnosis of sarcopenia, a low appendicular lean mass (<20 kg for men, <15 kg for women) or a low appendicular lean mass index (appendicular lean mass/height²; <7.2 kg/m² for men, <5.5 kg/m² for women) is often used.¹² According to ISCD position statements, total body DXA can be used in patients with obesity who are considering weight-loss regimens anticipated to result in weight loss greater than 10%.⁴

Key Learning Points

- Hip and spine DXA have been the standard of care for skeletal health assessments, but in 2026, many other DXA tools are currently used in clinical and research settings.
- TBS can be used to refine fracture risk assessment.
- FFI can be used to detect incomplete AFFs.
- A total body composition scan can assess fat and lean mass and is useful for diagnosing sarcopenia. It also helps monitor loss of fat and lean mass during weight loss.

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Osteoanabolic Therapies in Osteoporosis: When to Build Bone and How to Sequence Treatment

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify patients with osteoporosis at very high risk of fracture who would benefit from early osteoanabolic therapy.
- Discuss the available osteoanabolic therapies, explain their antifracture efficacy, and identify key factors to consider when choosing among them.
- Explain how osteoporosis drug sequences influence outcomes and the importance of antiresorptive consolidation after a course of osteoanabolic therapy.

Significance of the Clinical Problem

Osteoporosis affects more than half a billion people worldwide.¹ In 2019, 37 million fragility fractures occurred in people older than 55 years, an estimated 70 new fractures per minute.¹ Global projections indicate a doubling of hip fracture rates over the next 25 years, with high costs to health care systems, individuals, and their communities. Hip fractures are particularly problematic, with mortality rates of up to 24%, loss of independence

in 40%, and 33% of sufferers requiring assisted care in the first year.²

Hip fracture may be considered an end stage of skeletal fragility. In fact, a significant proportion of people with hip fractures in later life have experienced “sentinel fractures,” predominantly of the distal radius or humerus, in earlier decades.³ Modifying skeletal fragility by building new bone at a critical stage in disease progression may prevent this particularly feared complication of osteoporosis.

Drugs that modify bone and prevent fragility fractures are broadly grouped into antiresorptive and osteoanabolic therapies. While the former group of drugs suppresses bone remodeling and *retains existing bone*, osteoanabolic drugs target osteoblasts to *promote new bone formation*. This chapter discusses the use of various osteoanabolic therapies, the drug sequences that affect their outcomes, and clinical features to identify patients who would benefit from early use of osteoanabolic therapy.

Practice Gaps

- The osteoporosis field continues to grapple with a significant treatment gap. A large proportion of patients with fragility fractures and risk factors for bone loss (~70%-80% across different developed nations) do not

receive appropriate fracture-preventing therapies. Systems that quickly identify patients at risk of fracture and greater awareness of osteoporosis treatment options will help bridge this gap.

- Antiresorptive drugs are widely considered first-line therapy for osteoporosis. However, clinicians should recognize risk profiles in which osteoanabolic treatment yields superior outcomes compared with initial therapy.
- When initiating osteoanabolic therapy, it is essential to establish clear responsibility for timely subcutaneous administration, implement systems to monitor adherence, and plan for consolidation with antiresorptive therapy at the end of the treatment course.
- Drug sequence matters in osteoporosis. The impact of prior antiresorptive therapy on osteoanabolic treatment effectiveness is often underappreciated.
- Understanding the key principles of osteoanabolic therapy in clinical practice is important and will lead to broader, more effective application. Core principles guiding the use of osteoanabolic therapies can be distilled into 3 simple statements: go hard early, make it count, and remember that sequence matters.

Discussion

First-Line Use of Osteoanabolic Therapies: “Go Hard Early”

Osteoporosis is a progressive, incurable disease that begins decades before fragility fractures occur. At a microscopic level, microarchitectural deterioration is characterized by deficits in trabecular and cortical bone, including thinning, loss of connectivity, increased spacing of trabecular networks, and cortical porosity. Functionally, these deficits compromise bone strength by diminishing its stiffness and reducing its ability to resist everyday mechanical loads.⁴ By directly targeting these structural changes, osteoanabolic therapy is disease-modifying, rapidly

increasing bone mass, restoring microstructure, and thereby preventing fragility fractures.⁵

Clinical red flags of severe microarchitectural deterioration warrant attention. Patients at very high and/or imminent fracture risk may present with a combination of clinical features, as shown in the *Box*. These patients are likely to have significant microarchitectural decay, which would benefit from early, first-line osteoanabolic therapy.

Box. Clinical Features of Very High Fracture Risk*

- Fracture history: recent or multiple fragility fractures, vertebral fractures
- Fractures while receiving osteoporosis therapy
- Very low T-scores ≤ -3.0 SD on DXA bone mineral density scan
- Secondary causes including long-term glucocorticoid therapy
- High risk of falls
- Fracture risk that significantly exceeds country-specific treatment threshold

*Reflecting expert consensus from key international guidelines on osteoporosis therapy (US Endocrine Society Guidelines, RACGP Australian guidelines, UK National Osteoporosis Guideline Group).

There are currently 3 osteoanabolic drugs in clinical use: PTH analogues, teriparatide and abaloparatide, and a monoclonal antibody to sclerostin, romosozumab. PTH analogues primarily target remodeling-based bone formation with stimulatory effects on both osteoblasts and osteoclasts, favoring a net anabolic effect. Teriparatide (PTH 1-34), administered subcutaneously at 20 mcg daily for 18 to 24 months, reduced vertebral fractures by approximately 65% and nonvertebral fractures by approximately 50% compared with placebo.⁶ Similar benefits were observed with abaloparatide, a synthetic analogue of PTHrP (80 mcg daily), which reduced vertebral fractures by approximately 85% and nonvertebral fractures by approximately 40% over 18 months compared with placebo.⁷ Administered monthly, romosozumab (210 mg) led to an approximately 70% reduction in vertebral fractures and approximately 40% reduction in nonvertebral fractures when excluding Latin American participants (whose inherent risk of nonvertebral

fracture was low at baseline).^{8,9} In contrast to PTH analogues, romosozumab promotes modeling-based bone formation, in which osteoblast activity is uncoupled from osteoclast-mediated resorption. With this agent, new bone apposition occurs at both the cancellous and endocortical surfaces.¹⁰

In patients at very high risk of fracture, head-to-head trials indicate that osteoanabolic therapy is superior to antiresorptive therapy in improving bone mineral density (BMD) and preventing fractures. The pivotal VERO and ARCH trials included patients with prevalent vertebral fracture, significant osteoporosis on BMD assessment, and in general, a 10-year major osteoporotic fracture risk greater than 20% based on FRAX.^{11,12} In these high-risk groups, romosozumab and teriparatide were superior to alendronate and risedronate, respectively, with reductions in new vertebral fractures of around 50% and in clinical fractures of 30% to 40%. Smaller studies report greater improvements in BMD with romosozumab than with denosumab.¹³ A propensity-score matched, post hoc analysis of FRAME reported fewer vertebral fractures in those commencing treatment with romosozumab vs denosumab.¹⁴

Practical Considerations and Choice of Osteoanabolic Drug: “Make It Count”

Courses of osteoanabolic therapy are generally restricted to 18 to 24 months for PTH analogues and 12 months for romosozumab, administered in a single, continuous period per lifetime. This stems from historical concerns about a greater risk of osteosarcoma with prolonged use of PTH analogues and the concept of a transient “anabolic window.” With more than 20 years of experience, the osteosarcoma concern was not borne out in large-scale registry studies with teriparatide, and the FDA lifted the 24-month lifetime restriction in 2020.¹⁵

After a course of teriparatide, antifracture effects persist for up to 30 months, particularly among those transitioning to antiresorptive therapy.^{16,17} In extensions of FRAME and ARCH, denosumab or alendronate consolidated gains

in BMD and prolonged antifracture effects after romosozumab.^{8,12} A single dose of zoledronic acid was also effective for at least 2 years after a 12-month course of romosozumab.¹⁸ Conversely, in phase 2 studies, patients who did not sequence to an antiresorptive agent after romosozumab demonstrated a rapid decline in BMD, with a more gradual return to baseline in patients coming off teriparatide.^{19,20} Therefore, to “make it count,” timely administration of an antiresorptive agent, within days or weeks (not months) of the last dose of osteoanabolic agent, should be clearly planned.

Choice of osteoanabolic therapy depends on several factors, including clinical status, adverse effect profile, interpretation of safety signals for the individual, and patient preference. Choosing the best osteoanabolic agent depends on individual factors and on a careful, informed discussion between the clinician and the patient (*Table 1, following page*). The distinction between daily subcutaneous self-administration of PTH analogues and monthly administration of romosozumab by a health care professional is important. Teriparatide has been in clinical use for more than 2 decades, with more than 360,000 patient-years of experience in the United States alone. The wealth of experience with this agent may be attractive to patients.²¹ The cardiovascular safety signal with romosozumab, which led to a black-box warning by the FDA and other agencies, is another important consideration. Cardiovascular risk assessment before initiating therapy may be warranted. An in-depth discussion with the patient and shared decision-making about the best course of action are necessary to make this important choice.

Another practical consideration is to ensure a vitamin D-replete state before commencing osteoanabolic therapy, as new bone requires mineralization. PTH analogues differ in their effects on serum calcium. Teriparatide typically causes a transient increase in calcium at 4 to 6 hours after a dose, whereas this is less common with abaloparatide.⁷ This difference is due to differential PTH-receptor binding, with teriparatide having a greater stimulatory

Table 1. Differences Between Osteoanabolic Agents

Medication	Advantages	Disadvantages	Ideal Patient
Teriparatide (TPTD)	• Longest clinical experience • Robust safety data	• Daily subcutaneous injections • Contraindicated if cancer or RTX • Vasodilation effects (headaches, flashes)	• Very high fracture risk • Recent painful vertebral fracture • CV safety concerns
Abaloparatide (ABL)	• Slightly greater hip BMD effect than TPTD • Less calcemic than TPTD	• As with TPTD	• As with TPTD
Romosozumab (ROMO)	• Rapid BMD gains • Monthly administration	• CV safety signal • Caution in patients with previous MI/CVA	• Very high fracture risk • Multiple recent fractures, needing rapid BMD gain • No CV concerns

Abbreviations: RTX, radiation therapy; CV, cardiovascular; MI, myocardial infarction; CVA, cerebrovascular accident.

effect on bone resorption.²² Patients with unexplained hypercalcemia and/or elevated alkaline phosphatase should undergo appropriate investigation before commencing PTH analogues. By contrast, romosozumab decreases serum calcium levels, particularly in the first month, by up to 3%. Although this is rarely symptomatic, it is important to ensure normal calcium levels before therapy initiation.²³

Because osteoanabolic therapies are generally time-limited, initiation should be deliberate, adherence closely monitored, and posttreatment antiresorptive therapy clearly documented. Regular assessment of fractures, BMD, and clinical risk should guide ongoing management. A simple accountability tool, such as a dose checklist, can help ensure adherence and facilitate the transition to antiresorptive therapy at course completion.

Second-Line Use of Osteoanabolic Therapies: “Sequence Matters”

Although first-line osteoanabolic therapies for osteoporosis have been well studied in large randomized controlled trials, evidence on their second-line use is less robust. This is despite greater real-world use of these drugs as second-line therapies in patients who appear to “fail” on antiresorptive agents. Observational studies have

sought to address this evidence gap.^{24–26} However, these studies are limited by potential selection bias, insufficient statistical power to assess fracture differences, and reliance on BMD as the primary outcome.

These studies suggest that second-line osteoanabolic therapy yields diminished gains in BMD, particularly when prior antiresorptive therapy is prolonged. More potent bisphosphonates, such as alendronate, may have a greater blunting effect than weaker agents, such as risedronate, when followed by teriparatide.²⁷ BMD effects may also vary by site, with greater attenuation of gains and potential losses at the hip than at the spine in patients transitioning from antiresorptive to osteoanabolic therapy.^{24–26}

In patients previously treated with bisphosphonates, restoring bone turnover and promoting the formation and mineralization of new bone require longer treatment with PTH analogues (ie, a full 24-month course of teriparatide).^{28,29} However, there is no evidence that bisphosphonate washout periods are helpful.³⁰ Romosozumab may produce more rapid gains in BMD than teriparatide in bisphosphonate-pretreated patients, owing to its predominant effect on sites of modeling-based bone formation, distinct from remodeling sites suppressed by bisphosphonate activity.³¹ However, claims of

romosozumab's superiority in this context are premature given the lack of fracture data, the longer treatment time required for teriparatide, and gaps in understanding the effects of sequential drugs on BMD.

In patients switching from denosumab, anabolic effects may be offset by rebound increases in bone turnover. After 24 months of denosumab, patients who switched to teriparatide experienced an early decline in hip BMD, accompanied by increased bone turnover and reduced cortical volumetric BMD on high-resolution peripheral quantitative CT.^{32,33} Although hip deficits recovered by 24 months of teriparatide in this study, this sequence may result in sharper, more prolonged declines in BMD in those sequencing from longer-term denosumab to teriparatide.²⁵ Patients switching to romosozumab experience diminished gains even after just 1 year of denosumab.^{24,26} Studies have explored adding an osteoanabolic agent to continuing denosumab to avoid rebound following withdrawal. Although these strategies are off label and supported by limited safety data, early studies suggest greater spine BMD gains with combination approaches.^{25,34-36}

Switching between osteoanabolic therapies, or “cycling” (ie, additional courses of osteoanabolic therapies), is understudied and likely to be the

focus of future research. Early evidence suggests that switching from teriparatide to romosozumab may result in BMD gains, whereas switching in the opposite direction is not beneficial.^{24,37} Additional cycles of romosozumab may continue to lead to sequential gains over time.³⁷⁻³⁹ The FDA lifted the 24-month lifetime limit for teriparatide in 2020, and although early data showed a promising recapitulation of its anabolic effect on reuse, decisions should be personalized until stronger data emerge.⁴⁰

Sequence matters when using osteoanabolic agents as second-line therapy, and both the duration and type of prior antiresorptive treatment are important factors. For further information on the unique considerations of each sequence, see *Table 2*.

Clinical Case Vignettes

Case 1

A 68-year-old woman develops sudden midthoracic pain after bending to pick up laundry. Thoracolumbar X-ray demonstrates a compression fracture of the T8 vertebra.

Table 2. Considerations in the Second-Line Use of Osteoanabolic Therapies

Therapies	Key clinical issues	Practical strategies
BPs → TPTD	Anabolic response may be blunted, particularly with prolonged BP treatment	Longer duration of teriparatide out to 24 months may be warranted to achieve full benefits in BMD
BPs → ROMO	Anabolic response may be blunted, particularly with prolonged BP treatment	Spine bone mineral density is likely to improve but effects at hip may be particularly blunted compared to treatment-naïve
DMAb → TPTD	Rebound increase in bone turnover may occur, blunting the anabolic effect	• Avoid this sequence if possible • Bone turnover markers may be helpful to assess for rebound • Possible combination strategies, continuing denosumab may be warranted
DMAb → ROMO	Rebound increase in bone turnover may be seen, blunting the anabolic effect	• Spine bone mineral density may improve, but effects at hip may be particularly blunted • Bone turnover markers may be helpful to assess for rebound and possible combination strategies may be warranted

Abbreviations: BP, bisphosphonate; TPTD, teriparatide; DMAb, denosumab; ROMO, romosozumab.

DXA demonstrates severe osteoporosis, with the following values:

Lumbar spine T-score = -3.4 SD

Total hip T-score = -2.8 SD

Screening for secondary causes of osteoporosis excludes thyroid disease, malabsorptive disease, and myeloma. Kidney function is normal, and there is no history of cardiovascular or cerebrovascular disease. She has not previously received osteoporosis treatment and experienced menopause at age 52 years.

Relevant laboratory test results:

Serum calcium = 9.1 mg/dL (8.8 - 10.7 mg/dL)

(SI: 2.3 mmol/L [2.2 - 2.6 mmol/L])

Serum phosphate = 3.4 mg/dL (2.4 - 4.3 mg/dL)

(SI: 1.1 mmol/L [0.8 - 1.4 mmol/L])

25-Hydroxyvitamin D = 11 ng/mL (SI: 27.5 nmol/L)

Intact PTH = 105 pg/mL (SI: 11.1 pmol/L)

Which of the following statements is most accurate?

- Vitamin D deficiency is a contraindication to osteoanabolic therapy, and initial treatment with an antiresorptive agent is appropriate
- Vitamin D deficiency should be corrected before initiating osteoanabolic therapy
- This patient is not at high risk of fracture; osteoanabolic therapy should be reserved for later treatment
- Avoid romosozumab because vitamin D deficiency makes it less effective than antiresorptive therapy
- Additional secondary screening is warranted

Answer: B) Vitamin D deficiency should be corrected before initiating osteoanabolic therapy

This patient has severe osteoporosis with a recent vertebral fragility fracture and is at very high risk of refracture.^{41,42} Provided cost and availability do not pose barriers, osteoanabolic therapy is preferred over further antiresorptive therapy for this patient (thus, Answer C is incorrect). High-level evidence supports the superiority of

osteoanabolic therapy in improving BMD and reducing fractures in patients at high risk.^{11,12}

Deferring treatment in favor of an initial course of antiresorptive treatment may also diminish the efficacy of second-line osteoanabolic therapy.^{24,28}

Osteoanabolic therapy is not contraindicated in the presence of vitamin D deficiency, but a replete state is necessary before commencement (thus, Answer B is correct and Answer A is incorrect). Study participants in major osteoanabolic drug trials were supplemented with vitamin D, and a replete state was confirmed prior to randomization.^{6,8,12} In this case, the patient displays hyperparathyroidism secondary to vitamin D deficiency. Restoring a vitamin D–replete state would therefore be essential to reduce the risk of hypocalcemia and ensure ideal conditions for an optimal response to osteoanabolic therapy.

The efficacy of romosozumab is not specifically affected by vitamin D deficiency, unlike antiresorptive agents (thus, Answer D is incorrect). The primary consideration is safety. Patients may experience a decline in serum calcium of up to 3% within the first month after romosozumab administration.²³ Hypocalcemia is also a well-recognized adverse effect of denosumab, particularly in patients with preexisting vitamin D deficiency and/or kidney impairment.⁴³ Therefore, ensuring normal calcium and vitamin D levels before initiating osteoporosis therapy is not specific to romosozumab.

No further screening for secondary osteoporosis is warranted with exclusion of major secondary causes at this time. The patient's elevated PTH is secondary to vitamin D deficiency, and normal calcium levels make primary hyperparathyroidism unlikely (therefore, Answer E is incorrect).

Case 1, Continued

After a period of vitamin D supplementation, the patient's laboratory test results are as follows:

25-Hydroxyvitamin D = 36 ng/mL (SI: 90 nmol/L)

PTH = 49 pg/mL (SI: 5.2 pmol/L)

Which of the following is the most appropriate next step in this patient's management?

- A. Persist with vitamin D supplementation, aiming for a serum 25-hydroxyvitamin D >48 ng/mL (SI: >120 nmol/L) before considering osteoanabolic therapy
- B. A 36-month course of abaloparatide is indicated, given the patient's very high fracture risk
- C. A sequential osteoanabolic approach is indicated with 12 months of romosozumab followed by 18 months of teriparatide or abaloparatide
- D. Begin a 12-month course of romosozumab, with plans to commence antiresorptive therapy afterwards
- E. Start teriparatide and repeat a BMD assessment at 6 months to determine whether an early switch to denosumab may be warranted

Answer: D) Begin a 12-month course of romosozumab, with plans to commence antiresorptive therapy afterwards

Early initiation of osteoanabolic therapy is warranted in this patient at very high fracture risk. The plan described in Answer D is correct with the appropriate duration of romosozumab (ie, 12 months) and the required sequential consolidation step with an antiresorptive agent. Longer-term treatment with romosozumab (up to 24 months) was examined in a phase 2 study, but its anabolic effect diminishes over time, with the greatest effects seen at 12 months.²⁰ Without sequencing to an antiresorptive agent, romosozumab's effects decline within 6 to 12 months and quickly return to baseline, hence the need to "lock in gains" with an appropriate antiresorptive agent. Denosumab, alendronate, or zoledronic acid is appropriate for consolidation following osteoanabolic therapies. Evidence for raloxifene or menopausal hormone therapy is less robust following romosozumab, although there is some benefit to transitioning from teriparatide to raloxifene.^{44,45}

The patient is currently vitamin D replete with normalization of PTH. Therefore, there is no need to push 25-hydroxyvitamin D to 48 ng/mL before starting therapy. Doing so would unnecessarily delay fracture-risk reduction in a patient at very high risk (thus, Answer A is incorrect). However, maintaining normal vitamin D levels throughout treatment is necessary.

Abaloparatide has been studied for up to 18 months. Although the FDA's 24-month restriction has been lifted for teriparatide, it remains in place for abaloparatide (thus, Answer B is incorrect). At 18 months, abaloparatide significantly reduced new vertebral fractures compared with a double-blind placebo and produced substantial improvements in lumbar spine bone mineral density, similar to teriparatide.⁷ The teriparatide arm was openlabel and not powered for a head-to-head fracture comparison with abaloparatide.

Although appealing in theory, switching between osteoanabolic therapies has not been adequately studied. Early evidence suggests that switching from romosozumab to teriparatide is not beneficial, as BMD declines (thus, Answer C is incorrect), whereas switching in the opposite direction may be helpful.³⁷ However, it is too early to make recommendations about direct osteoanabolic drug sequences.

Achieving the maximal increase in BMD with teriparatide typically requires around 18 months of treatment in treatment-naïve patients and up to 24 months in those who have previously received bisphosphonate therapy.²⁸ Earlier assessment and sequence to denosumab at 6 months is not likely to reap the maximal benefit of this osteoanabolic agent (thus, Answer E is incorrect). If adherence declines or a patient develops intolerance, a different approach may be warranted, including switching therapies sooner.

Case 2

A 74-year-old woman with postmenopausal osteoporosis has been receiving denosumab every 6 months for the past 4 years. Despite being adherent to this regimen, she has sustained 2 new

vertebral fragility fractures in the last 18 months, and her most recent DXA shows a lack of further improvement over 12 months:

Lumbar spine T-score = -3.1 SD

Total hip T-score = -2.0 SD

Laboratory tests exclude significant abnormalities; she is vitamin D replete, and a repeat secondary osteoporosis screen is unremarkable.

She is concerned that her current treatment is no longer working and asks about stronger “bone-building” drugs.

Which of the following is the most appropriate next step in managing her osteoporosis?

- A. Stop denosumab and switch to teriparatide immediately to stimulate bone formation
- B. Continue denosumab for now and await a significant decline in BMD before considering an osteoanabolic agent
- C. Transition to romosozumab with the possibility of combining treatment with denosumab
- D. A washout period following denosumab is necessary before deciding on osteoanabolic therapy
- E. Abaloparatide is the drug of choice in this patient due to its reduced calcemic effect compared with teriparatide and romosozumab

Answer: C) Transition to romosozumab with the possibility of combining treatment with denosumab

This patient has experienced multiple fragility fractures despite ongoing treatment and adherence to denosumab. New fractures occurring during antiresorptive therapy are sufficient to classify this as “treatment failure,” and a significant decline in BMD is not required before considering an osteoanabolic agent (thus, Answer B is incorrect).

The complicating factor is that switching directly from denosumab to an osteoanabolic agent may attenuate BMD gains due to a rebound increase in bone turnover. Although romosozumab provides both anabolic and

antiresorptive activity, its antiresorptive effect alone is insufficient to reliably prevent rebound in patients transitioning from long-term denosumab.^{26,46} In this setting, close monitoring of bone turnover markers may be prudent, with a plan to either reintroduce denosumab during romosozumab therapy if rebound is detected or continue denosumab alongside the initiation of romosozumab in selected patients (Answer C). Both sequential-combination strategies have shown promising results in real-world studies, but evidence remains limited, particularly regarding safety and fracture outcomes.^{25,34-36} This represents an important evidence gap in current osteoporosis practice. Patients should therefore be counseled carefully about the uncertainties and the rationale for this approach.

A direct switch from denosumab to either teriparatide or no treatment (Answers A and D) risks a significant rebound in bone turnover, decline in BMD, and potential clinical complications, including spontaneous vertebral fractures.^{32,33,47} As teriparatide increases bone remodeling, transitioning directly from denosumab may amplify the rebound surge in bone resorption. Studies demonstrate a substantial initial loss in cortical and total BMD with this transition, reflected as an early decline at the hip.^{32,33} Continuing denosumab with the addition of teriparatide may increase spine BMD and represent a more effective approach.²⁵

Abaloparatide is associated with less hypercalcemia than teriparatide, whereas romosozumab may lower serum calcium.⁷ Abaloparatide has not been studied in patients pretreated with denosumab, and there is no evidence of its superiority in this context (thus, Answer E is incorrect).

Case 3

A 78-year-old man presents for review of his osteoporosis management. He has been taking alendronate, 70 mg weekly, for 5 years with excellent adherence. He experienced a vertebral compression fracture 6 years ago, but has had

no recent falls or fractures. His medical history includes type 2 diabetes and dyslipidemia, both reasonably controlled with metformin and a statin, respectively.

DXA results are as follows:

Lumbar spine (L1–L4) T-score = -3.1 SD (5% decline from last year)
 Femoral neck T-score = -2.7 SD
 Total hip T-score = -2.5 SD

Given his persistent osteoporosis and declining spine BMD despite bisphosphonate therapy, you arrange a comprehensive secondary screen, which is negative. This includes kidney function, calcium, phosphate, thyroid function, celiac serology, testosterone, PTH, serum protein electrophoresis, and vitamin D.

What is the most appropriate next step in his management?

- A. Continue alendronate for another 1 to 2 years and monitor BMD
- B. Stop alendronate for at least 6 months before considering osteoanabolic therapy (“washout period”)
- C. Discuss different osteoanabolic therapy options, including teriparatide or romosozumab
- D. Start abaloparatide or teriparatide, as romosozumab would be contraindicated given his cardiovascular risk profile
- E. Switch to denosumab, as it has proven hip fracture efficacy in men and is safer than osteoanabolic agents

Answer: C) Discuss different osteoanabolic therapy options, including teriparatide or romosozumab

This patient has severe osteoporosis (T-score, -3.1 SD) with a documented decline in BMD despite 5 years of alendronate. He is therefore at very high fracture risk and has experienced bisphosphonate “treatment failure.” International guidelines, including the US Endocrine Society guidelines, recommend an osteoanabolic agent for patients with very low T-scores and/or treatment

failure on a bisphosphonate.^{41,42,48,49} This approach is more potent than persisting with antiresorptive agents in addressing microarchitectural deterioration. There is also direct evidence supporting the efficacy of romosozumab in men with osteoporosis (Answer C).⁵⁰

Denosumab is not specifically safer than osteoanabolic therapy and lacks direct hip fracture efficacy data in men, although this may be extrapolated (thus, Answer E is incorrect). Due to the long residence time of bisphosphonates in bone and their incorporation into the bone matrix, there is no evidence that a washout period is helpful before transitioning to an osteoanabolic drug (Answer B is incorrect).

This man’s coexisting diabetes and dyslipidemia are not contraindications per se for romosozumab (thus, Answer D is incorrect). The cardiovascular safety concern with romosozumab stemmed from a numerical imbalance in major adverse cardiovascular events (MACE) in the ARCH trial compared with the active comparator, alendronate.¹² Subsequent readjudication and post hoc analyses confirmed this, but no increase in cardiovascular risk with romosozumab was observed in the placebocontrolled FRAME study.¹⁴ In light of these findings, regulators have issued blackbox warnings on the use of romosozumab in individuals with a history of myocardial infarction or stroke, but not in those with cardiovascular risk factors *alone*. An assessment of this patient’s overall cardiovascular risk, including glycemic control, lipid profile, and blood pressure, is appropriate before considering romosozumab.

Would romosozumab be preferred over PTH analogues in patients on bisphosphonates? In a 12-month study, romosozumab led to greater improvements in hip BMD than teriparatide in patients on prior bisphosphonates (with a duration of >3 years).³¹ However, these findings should be interpreted with caution in the absence of fracture data and the longer treatment time required for teriparatide (18–24 months in people on prior treatment). In a real-world study, greater improvements in BMD were demonstrated in

people transitioning from bisphosphonates to romosozumab than to teriparatide.⁵¹

Case 3, Continued

After discussion of the different drug options and careful evaluation of his cardiovascular risk profile, the patient embarks on a 12-month course of romosozumab.

He experiences a significant improvement in his BMD, with the following values:

Lumbar spine (L1–L4) T-score = −2.6 SD

Femoral neck T-score = −2.5 SD

Total hip T-score = −2.3 SD

This represents an approximate 10% improvement in lumbar spine bone density and a 5% improvement in total hip bone density with romosozumab.

What is the most appropriate next step in his management?

- A. No further treatment is required as his BMD has improved significantly
- B. Start teriparatide and continue for 18 months to maintain his gains
- C. Resume oral alendronate therapy
- D. Start denosumab
- E. Consider continuing romosozumab for another 6 to 12 months until osteopenia is achieved on BMD

Answer: D) Start denosumab

Antiresorptive therapy is essential after osteoanabolic therapy to “lock in” gains in BMD (thus, A is incorrect). Denosumab is an effective agent in this setting and has been shown to consolidate and augment the BMD increases and exert sustained antifracture efficacy after romosozumab.¹⁴

Denosumab is more effective than alendronate at suppressing bone turnover,⁴ and although these drugs have not been directly compared after a course of romosozumab, this patient previously experienced a decline in BMD on alendronate. Hence, denosumab (Answer D) would be the most

appropriate next step and would provide him with further antifracture protection, an important goal given his previous vertebral compression fracture. Ongoing treatment with romosozumab beyond 12 months would not provide sufficient ongoing anabolic effect and would be off label (thus, Answer E is incorrect). Sequencing from romosozumab to teriparatide is not recommended because this approach results in a decline in BMD gains (thus, Answer B is incorrect).

Key Learning Points

- Osteoanabolic therapies stimulate *new bone formation*, a mechanism distinct from that of antiresorptive agents. Unlike bisphosphonates and denosumab, which primarily reduce bone loss, osteoanabolic agents such as teriparatide, abaloparatide, and romosozumab actively promote bone formation and improve skeletal microarchitecture.
- Patients at *very high risk of osteoporotic fracture* require prompt clinical evaluation. Key red flags include recent fragility fractures, markedly low bone mineral density, glucocorticoid use, or a history of multiple fractures. These individuals are strong candidates for early initiation of osteoanabolic therapy.
- The selection of osteoanabolic therapy should be made through shared decision-making, taking into consideration previous therapy, the patient’s clinical condition, preferences, and tolerability.
- Treatment sequence matters. Starting with an anabolic agent followed by an antiresorptive therapy achieves greater and more durable BMD gains than the reverse sequence. Prior bisphosphonate use may blunt the response to osteoanabolic therapy. Romosozumab is more effective than PTH analogues in increasing BMD after antiresorptive agents.
- Osteoanabolic therapies have finite treatment windows and must be followed by antiresorptive therapy to preserve BMD and

reduce fracture risk. Regular assessment of fractures, BMD, and clinical risk should guide ongoing management.

- Important evidence gaps remain in osteoanabolic treatment strategies. These include the longterm durability of BMD gains after treatment cessation and the optimal sequencing or combination of anabolic and antiresorptive agents to maximize fracture

reduction. The use of osteoanabolic therapies in distinct cycles and direct osteoanabolic drug sequences remains to be clarified.

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Osteoporosis in Women With Breast Cancer

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Educational Objective

After reviewing this chapter, learners should be able to:

- Describe the incidence, risk factors, and prevention and treatment of osteoporosis and fragility fractures in premenopausal women with breast cancer.
- Describe the incidence, risk factors, and prevention and treatment of osteoporosis and fragility fractures in postmenopausal women with breast cancer.

Significance of the Clinical Problem

Breast cancer is the most common malignant disease in women and the second leading cause of cancer-related death among women aged 40 to 55 years in the United States, with more than 40,000 women dying of this disease each year. In the United Kingdom, breast cancer has the fifth-highest incidence rate in Europe and the seventh-highest in the world (95.0 new cases per 100,000).¹ Worldwide, breast cancer affects more than 1 in 10 women.

Early diagnosis and improved treatment regimens have significantly increased survival, thereby increasing the potential for long-term adverse effects of cancer treatments, including bone loss and fractures.² Skeletal homeostasis is maintained by coupled and balanced bone resorption and formation. Several local and

systemic factors regulate these processes, including estrogen, a key regulator of bone resorption. Physiologic decreases in estrogen levels after menopause lead to an imbalance between bone resorption and formation, increasing the risk of osteoporosis (low bone mineral density [BMD]) and fractures. Breast cancer and its therapies can exacerbate this risk. Systemic therapies for breast cancer can interfere with bone turnover, either by affecting gonadal steroid hormone production or by inhibiting peripheral aromatization into estrogen. In addition, some therapies for breast cancer may directly affect bone formation. Regardless of the underlying mechanism, patients with breast cancer are at increased risk for cancer treatment-induced bone loss (CTIBL).³

Practice Gaps

- A low percentage of women with breast cancer are identified as being at high risk for osteoporosis and fractures.
- Prevention and treatment rates are low among women with breast cancer at high risk for fragility fractures.
- There is limited awareness that adjuvant bisphosphonate treatment can, in addition to preventing osteoporosis, reduce the risk of bone recurrence.

Discussion

Treatment-Induced Osteoporosis in Premenopausal Women With Breast Cancer

Most breast malignancies are hormone responsive, and adjuvant endocrine therapy is routinely used to prevent breast cancer recurrence and death. Only a few studies have investigated the effects of chemotherapy in premenopausal women with hormone receptor–negative breast cancer, reporting a significantly increased fracture risk compared with that of control participants. Tamoxifen ($\pm$ GnRH analogues and chemotherapy) is the treatment of choice in premenopausal women with hormone-responsive breast cancer.⁴ In contrast to outcomes in postmenopausal women, the use of tamoxifen in premenopausal women with breast cancer is associated with a significantly increased fracture risk. The combination of GnRH analogues with tamoxifen in the treatment of premenopausal women with breast cancer has also been investigated. Compared with women on tamoxifen alone, those receiving combination treatment have a significantly increased risk of osteoporosis, although there are no available data on fracture risk.

Treatment-Induced Osteoporosis in Postmenopausal Women With Breast Cancer

In the past, tamoxifen was the treatment of choice for endocrine-responsive postmenopausal breast cancer and was found to preserve BMD in postmenopausal women, with fracture risk similar between postmenopausal tamoxifen users and nonusers.⁵ However, aromatase inhibitors have now replaced tamoxifen as the treatment of choice for hormone-responsive breast cancer in most postmenopausal women because of better efficacy and fewer serious adverse effects, such as uterine cancers and thromboembolic events.^{6,7} Because aromatase inhibitors prevent peripheral estrogen production, they suppress estrogen levels beyond those attained at natural menopause, thereby

accelerating bone loss and increasing fracture risk.⁸ In addition to contributing to a reduced quality of life, increased morbidity and treatment-induced fractures increase the health economic burden.⁹ A recent study reported that, compared with the general population, patients with breast cancer had fracture incidence rate ratios of 1.25 (95% CI, 1.23–1.28) and 1.18 (95% CI, 1.14–1.22) for hospitalization due to any bone fracture and hip fracture, respectively. These ratios remained significantly increased for 10 years.¹⁰ Women taking aromatase inhibitors were at higher risk of fracture than women taking tamoxifen (hazard ratio, 1.48; 95% CI, 0.98–2.22). Additionally, patients with breast cancer hospitalized for a bone fracture had a higher risk of death (hazard ratio, 1.83; 95% CI, 1.50–2.22) than those without a bone fracture.

Treatment-Related Fracture Risk in Premenopausal and Postmenopausal Women With Breast Cancer

The influence of chemotherapy on fracture risk in premenopausal women with hormone receptor–negative breast cancer has been poorly studied. A recent large-scale, case-control study showed a 2-fold higher fracture risk after chemotherapy than in healthy controls. Fracture risk with tamoxifen use depends on menopausal status. In premenopausal women with hormone-sensitive breast cancer, tamoxifen use increased fracture risk 2-fold compared with healthy controls, whereas postmenopausal women had no increased fracture risk.^{4,5} Aromatase inhibitor–associated bone loss (AIBL) leads to a marked increase in bone resorption, with a 2- to 4-fold increase in bone loss compared with physiologic postmenopausal BMD loss.¹¹ As a result, women receiving adjuvant aromatase inhibitor therapy for breast cancer are at increased risk for fractures, leading to increased morbidity and mortality.¹² Randomized controlled trials including aromatase inhibitor therapy for 5 years suggest an increased absolute fracture risk of around 10%, indicating that 1 in 10 women

will eventually fracture. However, these studies had stringent inclusion and exclusion criteria that may not reflect fracture risk in the unselected population seen in routine clinical practice. Real-world fracture risk has been investigated in several case-control studies, prescription-based analyses, single-center studies, and even in a recent randomized controlled trial. In the latter, the fracture incidence in women with breast cancer on an aromatase inhibitor was reported to be 18% to 20% after 5 years of follow-up, indicating that in clinical practice, about 1 in 5 women will sustain an aromatase inhibitor–related fracture.

After termination of aromatase inhibitor treatment, bone turnover normalizes and BMD can partially recover, but microarchitectural deterioration persists, leading to a persistently increased fracture risk. Recently, conflicting evidence has emerged regarding the extended duration of aromatase inhibitor treatment up to 10 years. For those advocating an increased duration of aromatase inhibitor treatment for up to 10 years, a further increased fracture risk, in addition to the 2% to 3% per year, must be considered.

Assessment of Osteoporosis-Related Fracture Risk

Recently, an updated position statement from 7 international bone and cancer societies evaluated fracture risk and included treatment recommendations for AIBL.^{3,13} After a systematic literature review of clinical prognostic risk factors for fracture in patients with breast cancer, an evidence-based medicine approach was used to determine when to initiate antiresorptive therapy for AIBL, the appropriate antiresorptive therapy, and follow-up/monitoring procedures. Several additional clinical risk factors have been validated in large, prospective, population-based studies in postmenopausal women and characterized by their effects on overall fracture risk, independent of age and BMD.

In addition to aromatase inhibitor therapy, factors that increase fracture risk in women with breast cancer include a T-score less than -1.5 , age older than 65 years, BMI less than 20 kg/m^2 , family

history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use for more than 6 months, rheumatoid arthritis, and smoking. Recent data suggest that BMD measurement alone should not be the sole criterion for determining fracture risk, and that an overall fracture risk assessment that combines risk factors provides a more accurate evaluation. Use of corticosteroids at a daily dose greater than 2.5 mg of prednisolone (or equivalent) for more than 3 months is an established risk factor based on data from nonmalignant disease settings. When combined with chemotherapy regimens, oral corticosteroid doses are typically higher and may negatively affect bone health over a shorter period. Finally, to identify and manage secondary causes of osteoporosis, complete baseline laboratory assessments should include serum measurements of calcium, phosphate, 25-hydroxyvitamin D, C-reactive protein, alkaline phosphatase, TSH, and gamma-glutamyl transpeptidase; complete blood cell count; creatinine clearance; and protein electrophoresis (serum and/or urine).

Regarding the prevention and treatment of AIBL, data from randomized clinical trials in more than 6000 patients suggest that denosumab and intravenous and oral bisphosphonates can effectively prevent AIBL in patients with breast cancer. Although most of these trials were not designed with a fracture prevention endpoint, data from the osteoporosis setting support the use of BMD improvements as a surrogate for fracture prevention.¹³

All patients starting aromatase inhibitor therapy should be advised to engage in moderate exercise, including resistance and weight-bearing activities. Although weight-bearing exercise benefits BMD, reductions in fracture risk have not been demonstrated. Regarding calcium and vitamin D, the International Osteoporosis Foundation recommends a daily intake of 1200 mg of calcium and 800 to 1000 international units of vitamin D for postmenopausal women (guidelines available at www.iofbonehealth.org). Older women, or those with reduced physical activity and sunlight exposure, may need higher levels of

these nutrients. For these individuals at high risk of fracture, measurement of 25-hydroxyvitamin D is recommended, and high-dose vitamin D supplementation is given if deficient. For other postmenopausal women receiving aromatase inhibitor therapy, a daily dose of at least 800 (up to 2000) international units of vitamin D is recommended to maintain replete vitamin D levels. A recent meta-analysis has underscored that vitamin D alone or with calcium supplementation is ineffective for preventing fractures in women with breast cancer.

For patients initiating aromatase inhibitor therapy, BMD measurement is advised. For patients with a T-score greater than -2.0 and no other fracture risk factors, BMD and risk status should be reassessed after 12 months. If no adjuvant antiresorptive therapy is initiated, an annual decrease in BMD of 5% to 10% should prompt investigation for secondary causes of bone loss, such as vitamin D deficiency, and initiation of antiresorptive treatment for fracture prevention. All patients initiating or receiving aromatase inhibitor therapy with any 2 of the following risk factors should receive antiresorptive therapy: T-score less than -1.5 , age older than 65 years, BMI less than 20 kg/m^2 , family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use for more than 6 months, and current or history of smoking. Any patient initiating or receiving aromatase inhibitor therapy with a T-score less than -2.0 at the spine, total hip, or femoral neck should receive antiresorptive therapy irrespective of other risk factors. Based on current evidence, subcutaneous denosumab (60 mg twice yearly; same dosage as for primary osteoporosis) and intravenous zoledronate (4 mg every 6 months; higher dosage than for primary osteoporosis) are the preferred agents for prevention and treatment of AIBL. Risedronate, 35 mg weekly, is the bisphosphonate with the strongest evidence for preventing AIBL. In all patients receiving oral bisphosphonate therapy, BMD should be monitored, and adherence assessed every 1 to 2 years. Periodic assessment of bone resorption

markers may provide a convenient, noninvasive measure of adherence to therapy.¹³ In case of poor adherence or BMD loss despite treatment, after 1 to 2 years, a switch to denosumab or intravenous bisphosphonate is recommended. For patients receiving denosumab, intravenous bisphosphonates, or other agents, BMD monitoring during therapy should be performed on an individualized basis and in accordance with local guidelines.

Patients receiving aromatase inhibitor therapy are at elevated risk of fracture for at least the duration of treatment. As a result, continuing antiresorptive therapy for as long as the patient is receiving an aromatase inhibitor (up to 5-10 years) is recommended. Currently, denosumab and zoledronate are the only antiresorptive agents with proven efficacy and safety in large, long-term, randomized controlled trials. Consequently, adverse effect profiles and management should be considered when selecting an antiresorptive agent to prevent or treat AIBL.

Disease Recurrence Prevention: Adjuvant Bisphosphonates

More than 35 randomized clinical trials have investigated the use of adjuvant bisphosphonates in early breast cancer, with varying results. Overall, treatment with these agents reduces bone metastases and breast cancer deaths in postmenopausal women, beyond their effects on bone health.¹⁴⁻¹⁷ The importance of this significant accompanying survival benefit of adjuvant bisphosphonate use in this patient population has led to their recommendation in treatment guidelines for bone health in cancer issued by the key professional bodies in oncology (European Society of Medical Oncology,¹⁸ American Society of Clinical Oncology¹⁹), as well as in several international interdisciplinary position statements.^{20,21} The optimal bisphosphonate, schedule, and duration of therapy to prevent disease recurrence have not been fully defined. Trials comparing agents both indirectly, as in the EBCTCG meta-analysis, and directly in one

large randomized trial suggest that intravenous zoledronate, daily oral ibandronate, and daily oral clodronate are similarly effective.¹⁷ Most guidelines recommend intravenous zoledronate, 4 mg, be started as soon as possible during (neo)adjuvant chemotherapy and continued thereafter every 6 months for at least 3 years. The intensive dosing schedules of zoledronate used in some clinical trials are not thought to be necessary and are associated with a much higher incidence of medication-related osteonecrosis of the jaw. Alternatively, the patient may choose between daily oral clodronate, 1600 mg daily, or oral ibandronate, 50 mg daily, as alternatives to intravenous therapy.¹⁷

Although multiple studies have confirmed the efficacy of denosumab in preserving bone health, it cannot be recommended for preventing disease recurrence in postmenopausal women with breast cancer.^{18,19} Results from the Austrian Breast and Colorectal Cancer Study Group-18 study of 3420 postmenopausal women with hormone-sensitive early breast cancer receiving aromatase inhibitor treatment suggested a 2.1% disease-free survival benefit with denosumab at 5 years compared with placebo, with a reported hazard ratio for disease-free survival of 0.83 and a median follow-up of 8 years.²² However, no significant effects on breast cancer mortality were observed. The international, multicenter, phase 3 D-CARE study, however, was unable to replicate these results, despite a study population at higher risk of recurrence than in the Austrian Breast and Colorectal Cancer Study Group-18. It randomly assigned 4509 women with high-risk early breast cancer to receive denosumab or placebo. The D-CARE trial found that denosumab did not improve disease-related outcomes for this population.²³ The conflicting results between these 2 studies and the validity of comparing them are the subject of debate, but contributors to these opposing conclusions are likely to be differences in study population, primary objectives, denosumab dose, and dosing schedule. Denosumab is not included as a recommended therapy in the ASCO–Ontario Health (Cancer Care Ontario)¹⁸ or ESMO guidelines.¹⁹

Conclusions and Future Directions

It is evident that, in addition to BMD, clinical risk factors can greatly influence fracture risk. Fractures are associated not only with morbidity and mortality, but also with high health care costs and increased health care use for several months after fracture occurrence. Additionally, vertebral and especially hip fractures are likely to result in prolonged disability and loss of independence, thereby increasing indirect costs. Improvements in fracture risk assessment can help identify patients who need pharmacologic intervention to improve bone health, thereby reducing fracture incidence. This chapter has discussed a previously presented evidence-based algorithm for assessing bone health in women with breast cancer and for initiating antiresorptive therapy in postmenopausal women with early-stage breast cancer, as well as in other postmenopausal women not being considered for aromatase inhibitor therapy and in premenopausal women receiving chemotherapy and ovarian suppression therapies. Based on current evidence, denosumab or zoledronate every 6 months for the duration of aromatase inhibitor therapy is recommended to prevent AIBL in postmenopausal women receiving adjuvant aromatase inhibitor therapy. Zoledronate is recommended when reducing disease recurrence is the priority, and denosumab is recommended when fracture risk is the dominant concern. Long-term efficacy and safety data for other agents continue to mature and should be considered as they become available.

In addition to the established risk factors, other potential risk factors in women with breast cancer include chemotherapy, glucocorticoid cotreatment, radiotherapy, low weight, and family history of hip fractures. Further studies examining the role of these factors are warranted. Furthermore, periodic (annual) assessment of patients with breast cancer with these potential risk factors may be prudent.

Overall, data from the AIBL setting, together with long-term use in treating postmenopausal osteoporosis, indicate that denosumab and bisphosphonates are safe and effective for preserving bone health during adjuvant endocrine therapy for breast cancer. In addition, emerging

anticancer benefits of bisphosphonates provide further rationale for proactively using these agents during adjuvant aromatase inhibitor therapy. Ongoing trials and the recent Oxford meta-analysis underscore the potential of oral and intravenous bisphosphonates to prevent bone recurrence of breast cancer and to improve breast cancer survival. Therefore, the role of antiresorptive agents in early breast cancer has been significantly expanded.

Clinical Case Vignettes

Case 1

A 38-year-old premenopausal woman with ER+, PR+, node-positive breast cancer receives chemotherapy followed by therapy with GnRH analogues and exemestane (aromatase inhibitor) for 5 years. Her BMD on DXA is -2.9 at the spine and -2.3 at the total hip.

Does the patient have an increased risk of fracture?

- A. No
- B. Slight increased fracture risk
- C. Moderate increased fracture risk
- D. High increased fracture risk

Answer: D) High increased risk of fracture

The patient is at increased risk of fracture because she received chemotherapy, glucocorticoid treatment to reduce adverse effects, a GnRH analogue, and an aromatase inhibitor (exemestane).

Case 1, Continued

Should treatment be advised?

- A. No
- B. Yes, start calcium and vitamin D supplementation
- C. Yes, start or increase resistance training
- D. Yes, start pharmacological treatment
- E. B, C, and D

Answer: E) B, C, and D

Calcium and vitamin D supplementation, along with resistance training, are the mainstay of osteoporosis treatment. According to international guidelines, pharmacological treatment is advised.

Case 2

A 57-year-old postmenopausal woman has ER+, PR+, node-negative breast cancer. Her mother had a hip fracture. She takes glucocorticoids, 7.5 mg daily, because of lupus and received an aromatase inhibitor for 5 to 8 years. Her BMD on DXA is -3.4 at the spine and -2.6 at the total hip.

Does the patient have an increased risk of fracture?

- A. No
- B. Slight increased fracture risk
- C. Moderate increased fracture risk
- D. High increased fracture risk

Answer: D) High increased fracture risk

The patient is at increased risk of fracture because she receives high-dosage glucocorticoids to treat lupus, she has a parental history of osteoporosis, she received an aromatase inhibitor for 5 to 8 years, and she has very low BMD.

Case 2, Continued

Should a pharmacological treatment be advised?

- A. No
- B. Yes, start calcium and vitamin D supplementation
- C. Yes, start or increase resistance training
- D. Yes, start a bisphosphonate or denosumab
- E. B, C, and D

Answer: E) B, C, and D

Calcium and vitamin D supplementation, along with resistance training, are the mainstay of osteoporosis treatment. According to international guidelines, pharmacological treatment is advised.

Case 3

A 62-year-old postmenopausal woman with ER++, PR++, 4-cm, node-positive breast cancer receives chemotherapy accompanied by glucocorticoid treatment to reduce adverse effects, followed by aromatase inhibitor therapy for 5 to 8 years.

Does the patient have an increased risk of recurrence?

- A. No
- B. Slight increased risk of recurrence
- C. Moderate increased risk of recurrence
- D. High increased risk of recurrence

Answer: D) High increased risk of recurrence

This patient is at increased risk of fracture because she received chemotherapy, glucocorticoids to reduce adverse effects, and an aromatase inhibitor for 5 to 8 years.

Case 3, Continued

Should bone-targeted treatment, regardless of BMD, be advised for preventing disease recurrence?

- A. No
- B. Yes, start calcium and vitamin D supplementation

- C. Yes, start denosumab
- D. Yes, start a bisphosphonate
- E. B, C, and D

Answer: E) B, C, and D

Calcium and vitamin D supplementation are the mainstay of osteoporosis treatment. According to international guidelines, pharmacological treatment with denosumab or bisphosphonates is advised.

Key Learning Points

- Premenopausal women with breast cancer who have chemotherapy-induced secondary amenorrhea or are receiving GnRH/tamoxifen or GnRH/aromatase inhibitor therapy are at increased risk of osteoporosis and fractures.
- Postmenopausal women with breast cancer who receive endocrine therapy with an aromatase inhibitor are at increased risk of osteoporosis and fractures.
- Adjuvant bisphosphonate treatment not only reduces the risk of osteoporosis and fractures but also lowers the recurrence risk.

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PTH Replacement Therapy for Chronic Hypoparathyroidism in Adults

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Evaluate and diagnose hypoparathyroidism (HypoPT), both postsurgical and nonsurgical.
- Manage hypoparathyroidism with conventional therapy and PTH replacement therapy as needed.
- Transition patients from conventional therapy to PTH therapy as indicated.

Significance of the Clinical Problem

HypoPT is a rare endocrine disorder with a prevalence of 6.4 to 37 per 100,000.¹⁻³ The diagnosis is confirmed by low serum corrected or ionized calcium, in the presence of low or inappropriately normal PTH levels.¹ Chronic HypoPT is associated with multiple long-term complications, including renal complications (nephrolithiasis, nephrocalcinosis, and impaired kidney function), cardiovascular abnormalities (prolonged QT-interval, cardiac arrhythmias, and hypocalcemic heart failure), and neurologic manifestations (paresthesia, cognitive impairment, and seizures).⁴ Additional manifestations include

cataracts, increased susceptibility to infections, and increased all-cause mortality.⁵

The first-line treatment for chronic HypoPT is conventional therapy with active vitamin D and calcium supplements. Recently, the US FDA and the European Medicines Agency approved the long-acting PTH analogue, palopegteriparatide, as a therapeutic option for adults with chronic HypoPT for whom conventional therapy fails.⁶ Palopegteriparatide has been shown to correct hypocalcemia, sustain normocalcemia, normalize urinary calcium and serum phosphorus levels, and improve quality of life (QoL). Kidney function also improves dramatically with palopegteriparatide, allowing successful discontinuation of conventional therapy in most patients.^{1,7-9} The phase 2 clinical trial evaluated patient-reported outcomes using the HypoPT Patient Experience Scales (HPES) and the Short-Form Health Survey (SF-36v2) through week 110. Palopegteriparatide was associated with significant improvements in disease-specific symptoms, daily functioning and well-being, and general health-related QoL.¹⁰ Furthermore, data from the phase 3 PaTHway trial on bone mineral density (BMD) showed that the mean BMD Z-scores decreased from the abnormally high values toward age- and sex-matched norms from baseline to week 52. The skeletal changes observed with palopegteriparatide are consistent with restoration of normal bone remodeling.¹¹

Practice Gaps

- Determining the reversibility of long-term complications of HypoPT with PTH replacement therapy.
- There is limited understanding of fracture risk in patients with chronic HypoPT among premenopausal and postmenopausal women and among men younger and older than 50 years.
- The effects of PTH replacement on neuropsychiatric and cognitive function in patients with chronic HypoPT need further research.

Discussion

Conventional therapy with calcium supplementation and active vitamin D remains the first-line treatment for chronic HypoPT with a goal of maintaining serum-corrected calcium levels in the low-normal range or just below the normal reference range while normalizing serum phosphorus, magnesium, and urinary calcium levels.

Wide fluctuations in serum calcium levels remain a limitation of conventional therapy, as oral calcium and calcitriol are associated with an increased risk of hypercalcemia. Patients often experience persistent hypocalcemic symptoms, including numbness, tingling, and muscle cramps, as well as cognitive impairment, and these symptoms may persist despite achieving serum calcium levels near the normal reference range. The high pill burden associated with conventional therapy further compromises adherence and QoL.

Conventional therapy does not address the underlying PTH deficiency and cannot adequately prevent multisystem complications. Hyperphosphatemia may persist despite dietary modifications, phosphate binders, and reductions in active vitamin D because the absence of PTH impairs renal phosphate excretion.

Hypercalcinuria may remain problematic, with urinary calcium levels exceeding 250 to 300 mg/24 h despite modifications to conventional therapy and the introduction of thiazide diuretics. Persistent hypercalcinuria may increase the

risk of nephrocalcinosis, nephrolithiasis, and progressive kidney impairment. The 2022 international HypoPT guidelines recommend conventional therapy as first-line therapy (weak recommendation, low-quality evidence), but acknowledge that PTH replacement should be considered when conventional therapy proves unsatisfactory.¹² This represents a paradigm shift in recognizing HypoPT as an endocrine deficiency disorder amenable to hormone replacement, similar to other classic endocrine diseases.

Palopegteriparatide is the only PTH replacement therapy currently approved for chronic HypoPT in adults. The 2025 best practice recommendations emphasize that palopegteriparatide is an important therapeutic advance and should be considered when conventional therapy is inadequate or not tolerated.¹ The revised European Society of Endocrinology guidelines similarly recognize that PTH replacement therapy reduces pill burden, improves biochemical parameters, and may improve QoL.

Palopegteriparatide is initiated at 18 mcg subcutaneously daily, with a 33% reduction in the active vitamin D dose and close monitoring of serum calcium adjusted for albumin.¹

Because palopegteriparatide has a long half-life of 60 hours, the dose is not adjusted before day 7. If serum calcium is low, the calcium supplement and/or active vitamin D doses can be increased. If hypocalcemia persists beyond day 7, the palopegteriparatide dose can be increased in 3 mcg increments. If serum calcium is normal, the active vitamin D and calcium supplement doses can be decreased gradually, aiming to discontinue active vitamin D and reduce the calcium supplement dose to 600 mg daily or less. If serum calcium is high, active vitamin D can be reduced or stopped, and the calcium supplement can be gradually tapered and discontinued. If hypercalcemia persists in the absence of calcium and active vitamin D, the palopegteriparatide dose can be reduced by 3 mcg every 7 days. The minimum palopegteriparatide dosage is 6 mcg daily, and the maximum in clinical trials was 60 mcg daily.

The safety profile of palopegteriparatide has been well characterized across multiple trials. Most treatment-emergent adverse events are mild or moderate and include injection-site reactions, nausea, headaches, and postural hypotension. Data from phase 2 and phase 3 trials with palopegteriparatide demonstrated that more than 90% of individuals achieved independence from conventional therapy, and more than 80% met the multicomponent primary endpoint, with normalization of 24-hour urinary calcium excretion while maintaining normal serum calcium and phosphorus. There were clinically meaningful improvements in kidney function and health-related QoL. Palopegteriparatide was generally well-tolerated with no new safety signals identified.

If palopegteriparatide is unavailable, teriparatide can be used, often in combination with conventional therapy, in multiple daily doses or via a subcutaneous pump, because its half-life is only 1 hour. Teriparatide use in HypoPT is off-label and not approved for this indication.

Clinical Case Vignettes

Case 1

A 35-year-old man (BMI = 27.5 kg/m²) with autosomal dominant hypocalcemia type 1 (ADH1) due to a likely pathogenic *CASR* variant (c.2482A>C; p.Thr828Pro) presents with persistent hypocalcemia, despite large doses of conventional therapy. Baseline evaluation shows hypocalcemia, hyperphosphatemia, low PTH level, hypercalciuria, hypomagnesemia, and hypokalemia. His course is complicated by frequent seizures, nephrocalcinosis, recurrent nephrolithiasis, and stage 3 chronic kidney disease (Table). Despite treatment with calcium carbonate and calcitriol, biochemical control remains suboptimal. Palopegteriparatide is initiated at 18 mcg daily and is gradually titrated to 27 mcg daily after 6 months, reaching 60 mcg daily by month 52. By month 52, the patient has improved serum calcium, reduced urinary calcium excretion,

Parameter	Conventional therapy	52 Months after starting palopegteriparatide, 60 mcg daily	Reference range
Treatments	Calcium carbonate, 3 g daily Calcitriol, 0.5 mcg 3x/week + 0.75 mcg 4x/week	Calcium carbonate, 4 g daily Calcitriol, 0.25 mcg daily	...
Corrected calcium	7.28 mg/dL (SI: 1.82 mmol/L)	8.52 mg/dL (SI: 2.13 mmol/L)	8.6-10.4 mg/dL (SI: 2.15-2.60 mmol/L)
Phosphorus	4.71 mg/dL (SI: 1.52 mmol/L)	4.39 mg/dL (SI: 1.42 mmol/L)	2.2-5.1 mg/dL (SI: 0.71-1.65 mmol/L)
PTH	<5.6 pg/mL (SI: <0.6 pmol/L)	<5.6 pg/mL (SI: <0.6 pmol/L)	15-65 pg/mL (SI: 1.6-6.9 pmol/L)
Magnesium	2.09 mg/dL (SI: 0.86 mmol/L)	2.29 mg/dL (SI: 0.94 mmol/L)	1.6-2.6 mg/dL (SI: 0.66-1.07 mmol/L)
25-Hydroxyvitamin D	48.4 ng/mL (SI: 121 nmol/L)	33.2 ng/mL (SI: 83 nmol/L)	≥30 ng/mL (SI: ≥75 nmol/L)
Urinary calcium	129 mg/24 h	69 mg/24 h	<250 mg/24 h (SI: <6.25 mmol/24 h)
Urinary creatinine	533 mg/24 h	709 mg/24 h	...
Serum creatinine	2.21 mg/dL (SI: 195 μmol/L)	2.05 mg/dL (SI: 181 μmol/L)	0.76-1.32 mg/dL (SI: 67-117 μmol/L)
Estimated GFR	38 mL/min per 1.73 m ²	43 mL/min per 1.73 m ²	~90-120 mL/min per 1.73 m ² (estimated)

and improved kidney function. He has had no kidney stones since starting palopegteriparatide.

Which biochemical profile is most consistent with ADH1 due to an activating variant in the CASR gene?

- A. Hypocalcemia, elevated PTH, hypophosphatemia, hypercalciuria
- B. Hypocalcemia, low or inappropriately normal PTH, hyperphosphatemia, hypercalciuria
- C. Normal calcium, normal PTH, hyperphosphatemia, hypercalciuria
- D. Hypocalcaemia, elevated PTH, hyperphosphatemia, hypercalciuria

Answer: B) Hypocalcemia, low or inappropriately normal PTH, hyperphosphatemia, hypercalciuria

ADH1 is characterized by hypocalcemia, low or inappropriately normal PTH, hyperphosphatemia, and hypercalciuria.

Case 1, Continued

Which complication is strongly associated with persistent hypercalciuria during conventional therapy in patients with ADH1?

- A. Osteoporosis
- B. Nephrocalcinosis and nephrolithiasis
- C. Hyperparathyroidism
- D. Cardiac arrhythmia

Answer: B) Nephrocalcinosis and nephrolithiasis

Conventional therapy increases the risk of nephrocalcinosis and nephrolithiasis by exacerbating hypercalciuria in patients with ADH1 in the absence of PTH.

Case 2

A 43-year-old woman with postsurgical HypoPT has been treated with conventional therapy requiring high doses of calcium supplements (600 mg of calcium citrate 4 times daily) and calcitriol (0.25 mcg 4 times weekly) for approximately 5 years. Despite this therapy,

she remains symptomatic, with severe fatigue, headaches, cognitive dysfunction (brain fog), irritability, depressive symptoms, and paresthesias. These symptoms necessitate frequent rescue calcium supplementation and are accompanied by marked fluctuations in serum calcium levels, ranging from hypocalcemia to hypercalcemia. She has been unable to continue working and is now on disability. At age 45 years, treatment with palopegteriparatide is initiated at 18 mcg daily and is gradually uptitrated to 27 mcg daily over 32 months with successful discontinuation of conventional therapy. She states that PTH therapy “has given me back my life,” and she has been able to return to work. The *Figure (following page)* illustrates the changes in corrected calcium levels before and after palopegteriparatide therapy.

Which patient-reported outcomes improved most significantly after transitioning to palopegteriparatide in patients with chronic HypoPT in phase 2 and phase 3 clinical trials?

- A. Physical and cognitive symptom domain scores as measured by HPES and SF-36
- B. Bone mineral density
- C. Risk of cardiovascular events
- D. All of the above

Answer: A) Physical and cognitive symptom domain scores as measured by HPES and SF-36

Palopegteriparatide demonstrated significant improvements from baseline in disease-specific symptoms and in effects on daily functioning and well-being at week 12, with these improvements sustained through week 110.

Case 2, Continued

What is the recommended strategy for transitioning a patient with chronic HypoPT from conventional therapy to palopegteriparatide?

- A. Initiate palopegteriparatide at 18 mcg daily and titrate based on serum calcium level, with gradual discontinuation of calcium supplements and active vitamin D

- B. Abruptly discontinue all conventional therapy and start high-dosage palopegteriparatide
- C. Add palopegteriparatide without adjusting conventional therapy
- D. Use only in patients with kidney failure

Answer: A) Initiate palopegteriparatide 18 mcg daily and titrate based on serum calcium level, with gradual discontinuation of calcium supplements and active vitamin D

According to the 2025 Best Practice Recommendations on HypoPT management, palopegteriparatide is initiated at a dose of 18 mcg subcutaneously daily with titration based on the following recommendation:

- a. If albumin-corrected serum calcium is below the target range, increase palopegteriparatide by 3 mcg every 7 days

- Before 7 days,* increase calcium and active vitamin D

- b. If albumin-corrected serum calcium is normal, continue palopegteriparatide to day 7*

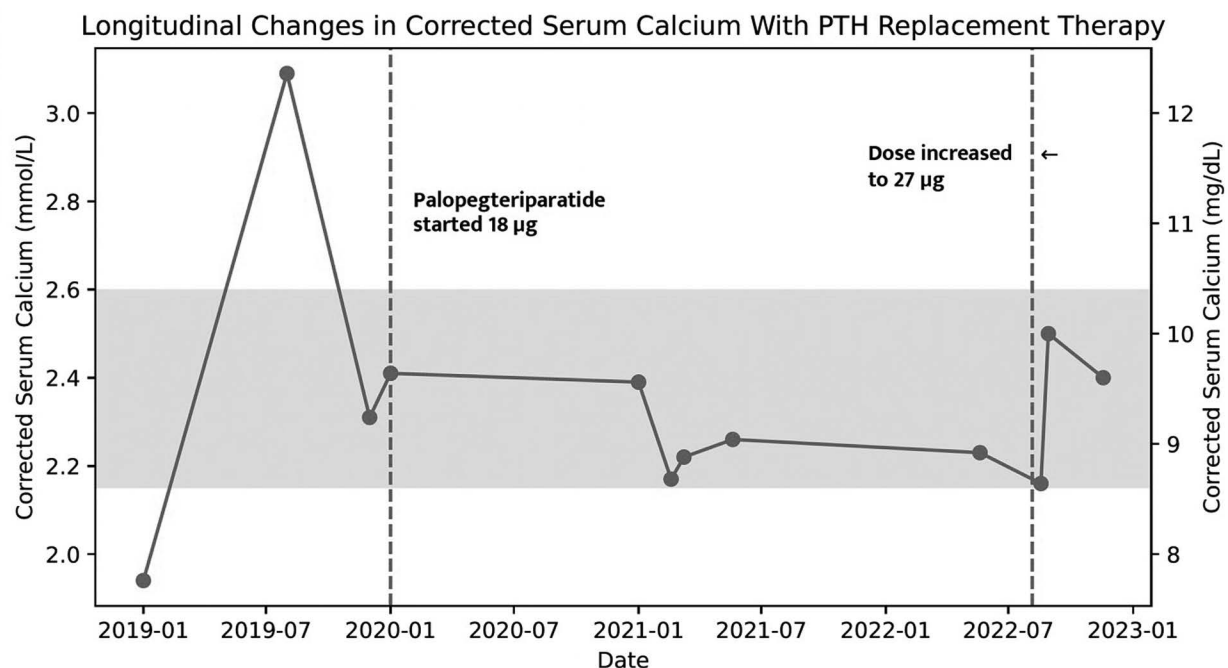
- At day 7,* decrease active vitamin D and increase palopegteriparatide by 3 mcg daily
- If not taking active vitamin D, decrease calcium by 1500 mg daily and increase palopegteriparatide by 3 mcg

- c. If albumin-corrected serum calcium is high, stop or decrease active vitamin D

- If not taking active vitamin D, decrease calcium
- If off active vitamin D and calcium, decrease palopegteriparatide

* Note: because palopegteriparatide has a 60-hour half-life, adjustments in the dosage are not made sooner than every 7 days.

Figure. Longitudinal Changes in Corrected Serum Calcium With PTH Replacement Therapy



[Color—Print (Color Gallery page CG6) or web & ePub editions]

Case 2, Continued

Which of the following clinical scenarios would most strongly support transitioning from conventional therapy to PTH replacement therapy?

- A. Serum calcium of 8.5 mg/dL (reference range, 8.6-10.4 mg/dL) on calcium carbonate, 1500 mg daily
- B. Persistent hypocalcemic symptoms despite adequate conventional therapy doses
- C. Patient preference for injectable therapy over oral medications
- D. Mild hyperphosphatemia of 4.8 mg/dL (reference range, 2.2-5.1 mg/dL)

Answer: B) Persistent hypocalcemic symptoms despite adequate conventional therapy doses

PTH replacement therapy should be considered when conventional therapy is unsatisfactory. Key indications include persistent hypocalcemic symptoms despite biochemical control, inability to maintain target serum calcium, hypercalciuria with risk of nephrocalcinosis or nephrolithiasis, refractory hyperphosphatemia, or an unacceptable pill burden affecting QoL.

Case 2, Continued

When transitioning a patient from conventional therapy to PTH replacement, which medication adjustment is most appropriate?

- A. Increase calcium supplementation to prevent hypocalcemia
- B. Continue calcitriol at the same dosage indefinitely

- C. Gradually reduce or discontinue calcium and active vitamin D
- D. Add a thiazide diuretic to enhance calcium retention

Answer: C) Gradually reduce or discontinue calcium and active vitamin D

When initiating PTH replacement therapy, conventional therapy with calcium and active vitamin D can be reduced or gradually discontinued. In clinical trials, patients who achieve independence from conventional therapy require 600 mg or less of elemental calcium daily and no active vitamin D. The transition should be gradual, with close monitoring of serum calcium.

Key Learning Points

- PTH replacement therapy should be considered in adult patients with chronic HypoPT for whom conventional therapy fails.
- When managing chronic HypoPT, aim to relieve symptoms of hypocalcemia while avoiding hypercalcemia, hypercalciuria, and hyperphosphatemia. The goal is to maintain serum-corrected calcium within the low-normal reference range or just below it.
- Aim to preserve kidney function and avoid the development of nephrolithiasis and/or nephrocalcinosis.
- Evaluate and aim to improve the patient's quality of life.

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Hypophosphatasia in Adults: Recognizing, Diagnosing, and Treating a Multisystem Disease

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the pathophysiology of hypophosphatasia (HPP) and its clinical manifestations in adults.
- Apply diagnostic criteria to identify adults with HPP and understand common diagnostic challenges.
- Describe evidence-based treatment options for adults with HPP.

Significance of the Clinical Problem

Hypophosphatasia (HPP) is an inherited metabolic disease caused by loss-of-function variants in the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP), the isoenzyme responsible for alkaline phosphatase activity in both bone and liver.¹⁻⁴ Historically regarded as a rare pediatric skeletal dysplasia, HPP is now recognized as a multisystem disorder that frequently presents in adulthood with heterogeneous and often nonspecific manifestations.⁴⁻⁷ Diagnostic delay is common, often exceeding a decade, reflecting limited clinician awareness and the protean nature of the disease in adults.⁸

In adults, manifestations extend beyond skeletal fragility to include dental disease, nephrocalcinosis, chondrocalcinosis, chronic musculoskeletal pain, fatigue, and muscle weakness.^{7,9-11} These features overlap with common conditions such as osteoporosis, fibromyalgia, and degenerative joint disease, contributing to misdiagnosis and inappropriate therapy.¹²⁻¹⁴ Notably, antiresorptive therapies commonly used for presumed osteoporosis may worsen skeletal outcomes in HPP, including increased risk of atypical femoral fractures and impaired fracture healing.^{15,16}

Accurate diagnosis of HPP has important clinical implications. Identification may allow access to targeted therapy with enzyme replacement, provide a unifying explanation for longstanding symptoms, guide surveillance and family counseling, and prevent exposure to potentially harmful treatments.^{1,2,13} Increasing clinician awareness of HPP in adults is therefore essential.

Practice Gaps

- Health care providers' limited awareness of HPP in adults.
- Difficulty recognizing nonspecific symptoms as manifestations of HPP.
- Challenges in interpreting low or low-normal alkaline phosphatase (ALP) values.
- Limited familiarity with diagnostic criteria for HPP and treatment options in adults.

Discussion

Pathophysiology

The *ALPL* gene encodes TNSALP, a ubiquitous ectoenzyme that hydrolyzes several physiologic substrates, including inorganic pyrophosphate (PPi), pyridoxal-5'-phosphate (PLP)—the principal circulating vitamin B₆ vitamers—and phosphoethanolamine (PEA).²⁻⁴ Deficient TNSALP activity leads to accumulation of PPi, a potent inhibitor of hydroxyapatite formation, resulting in osteomalacia, impaired mineralization, and delayed fracture healing.^{2,4} PLP elevation reflects impaired vitamin B₆ metabolism and is most prominent in severe phenotypes, although it can also support diagnosis in adults.^{17,18} Beyond mineralization, TNSALP has been implicated in mitochondrial energetics and related cellular bioenergetic pathways, providing mechanistic insight into muscle weakness, fatigue, and chronic pain observed in adults with HPP.¹⁹⁻²²

Clinical Manifestations in Adults

HPP in adults is characterized by substantial phenotypic variability.⁵⁻⁷ Common manifestations include:^{13,23-25}

- Recurrent metatarsal stress fractures and atypical femoral fractures
- Chronic musculoskeletal pain and fatigue
- Dental disease with premature tooth loss
- Chondrocalcinosis and pseudogout
- Nephrolithiasis or nephrocalcinosis
- Reduced physical function and quality of life

Data from the Global HPP Registry demonstrate that dental disease, musculoskeletal impairment, and pain are common in adults, with multisystem involvement often present even in “mild” disease.^{7,9}

Biochemical Presentation

Persistently low serum ALP is the biochemical hallmark of hypophosphatasia.^{2,13,14} However, ALP values may fall within the low-normal

range in adults with HPP for several reasons.²³⁻²⁶ Total ALP activity reflects contributions from TNSALP-derived isoenzymes (bone and liver), as well as intestinal, placental, or tumor-associated isoenzymes.²³⁻²⁶ Conditions that transiently increase bone or liver ALP, such as hyperparathyroidism, hyperthyroidism, recent fractures, bone-anabolic therapy, or liver and biliary disease, may raise total ALP into the reference range and mask underlying TNSALP deficiency.^{14,23-26}

In addition, substrate-specific defects in TNSALP have been described. Some *ALPL* variants can preserve catalytic activity toward artificial substrates (eg, p-nitrophenyl phosphate) used in routine ALP assays under nonphysiologic conditions, while demonstrating impaired hydrolysis of physiologic substrates (PPi, PLP, PEA).^{17,27} As a result, patients with clinically meaningful enzyme dysfunction may exhibit borderline or even “normal” total ALP activity.

Measurement of serum PLP and urinary PEA (and PPi, when available) supports the diagnosis by demonstrating impaired TNSALP activity.^{14,18,28} However, substrate testing has important limitations in adults. PLP is light-sensitive and influenced by dietary vitamin B₆ intake, supplementation, and kidney function; normal PLP levels, therefore, do not exclude HPP.^{14,18} Urinary PEA is a specific but variable marker of impaired TNSALP activity and does not correlate with disease severity.^{14,28} Accordingly, expert consensus emphasizes that biochemical substrate testing and genetic testing are complementary and should be performed together whenever feasible, rather than ordered sequentially.^{13,14}

Genetics and Prevalence

Nearly 500 *ALPL* variants have been identified, with both autosomal dominant and recessive inheritance patterns.^{5,6,29,30} Penetrance and expressivity are highly variable, even within families.⁶ Population-based studies now indicate that HPP in adults may be far more common than previously appreciated. Analyses from large

biobanks, including UK Biobank and BioVU, suggest that pathogenic or likely pathogenic *ALPL* variants may be present in approximately 1 in 175 to 1 in 350 to 500 individuals, many of whom exhibit mild, atypical, or incomplete phenotypes.³¹⁻³³

Importantly, genotype, residual enzymatic activity, and substrate levels correlate poorly with clinical severity in adults. While some heterozygous variants may exert dominant-negative effects, genotype alone does not reliably predict age of onset, skeletal burden, or extraskeletal manifestations.^{5,6,32,34} Diagnosis, therefore, requires integration of clinical features, biochemical findings, and genetic data.

Radiographic Findings

Radiographic manifestations in adults may include:^{7,10,12,15}

- Pseudofractures, particularly of the lateral femoral cortex
- Recurrent metatarsal fractures
- Chondrocalcinosis and calcific periarthritis
- Nephrocalcinosis or kidney stones

DXA is unreliable for fracture risk assessment in HPP; despite the potential for osteomalacia, lumbar spine bone mineral density (BMD) is often preserved or elevated.^{10,11}

Diagnostic Criteria for HPP Adults

International working group criteria require persistently low ALP plus either 2 major criteria, or 1 major and 2 minor criteria.¹³

Major criteria include identification of pathogenic or likely pathogenic *ALPL* variants, elevated TNSALP substrates (PLP, PEA, or PPi if available), atypical femoral fractures, and recurrent metatarsal fractures.¹³ Minor criteria capture common but less specific manifestations of adult hypophosphatasia and include:¹³

- Poorly healing fractures
- Chronic musculoskeletal pain

- Early, atraumatic loss of primary or permanent teeth
- Chondrocalcinosis or pseudogout
- Nephrocalcinosis or kidney stones

Patients may enter the diagnostic pathway for HPP through several distinct clinical scenarios (a suggestive phenotype, persistently low ALP, or an incidental genetic finding), and evaluation should converge on an integrated assessment of phenotype, biochemistry, and genotype (*Figure, following page*).^{13,14}

Treatment

Management includes supportive, multidisciplinary care and avoidance of harmful therapies.

Antiresorptive agents should generally be avoided due to increased risk of atypical femoral fractures and concerns regarding fracture healing in HPP.^{15,16}

Asfotase alfa, a recombinant TNSALP, is approved for pediatric-onset HPP in the United States and has demonstrated benefits in adults with pediatric-onset disease, including improved physical function, pain, and quality of life.³⁵⁻³⁸ Emerging real-world and registry data suggest potential benefits in selected adults, including improved fracture healing and functional outcomes.^{35,36,38,39}

Clinical Case Vignettes

Case 1

A 68-year-old woman is referred for evaluation of osteoporosis after DXA demonstrated severe bone loss at the distal radius and low bone density at the femoral neck (T-scores -3.9 and -2.6 , respectively), with relatively preserved lumbar spine density. She reports a single metatarsal fracture as a teenager. Alendronate had been prescribed, but she was hesitant to initiate therapy. Review of previous laboratory data revealed persistently borderline-low ALP activity ranging from 34 to 37 U/L (0.57 to 0.62 $\mu\text{kat/L}$) over the past decade (reference range, 35-130 U/L [0.58-2.17 $\mu\text{kat/L}$]).

She has a history of chronic musculoskeletal pain beginning in early adulthood, along with migraines and anxiety, and remains physically active with yoga. She has no medical conditions or medication exposures known to suppress ALP activity, including no exposure to glucocorticoids, antiresorptive agents, or hormone replacement therapy. Current medications include calcium supplementation (500 mg daily). Dental history includes multiple crowns and one extraction, with no premature tooth loss. Family history is notable for a father who became edentulous in his 50s and sustained a femur fracture, and a son with fibromyalgia, multiple musculoskeletal injuries, and hip replacement at age 31 years.

Laboratory evaluation shows high-normal serum calcium and phosphate; normal PTH, 25-hydroxyvitamin D, TSH, and serum protein

electrophoresis; and mildly elevated 24-hour urinary calcium excretion.

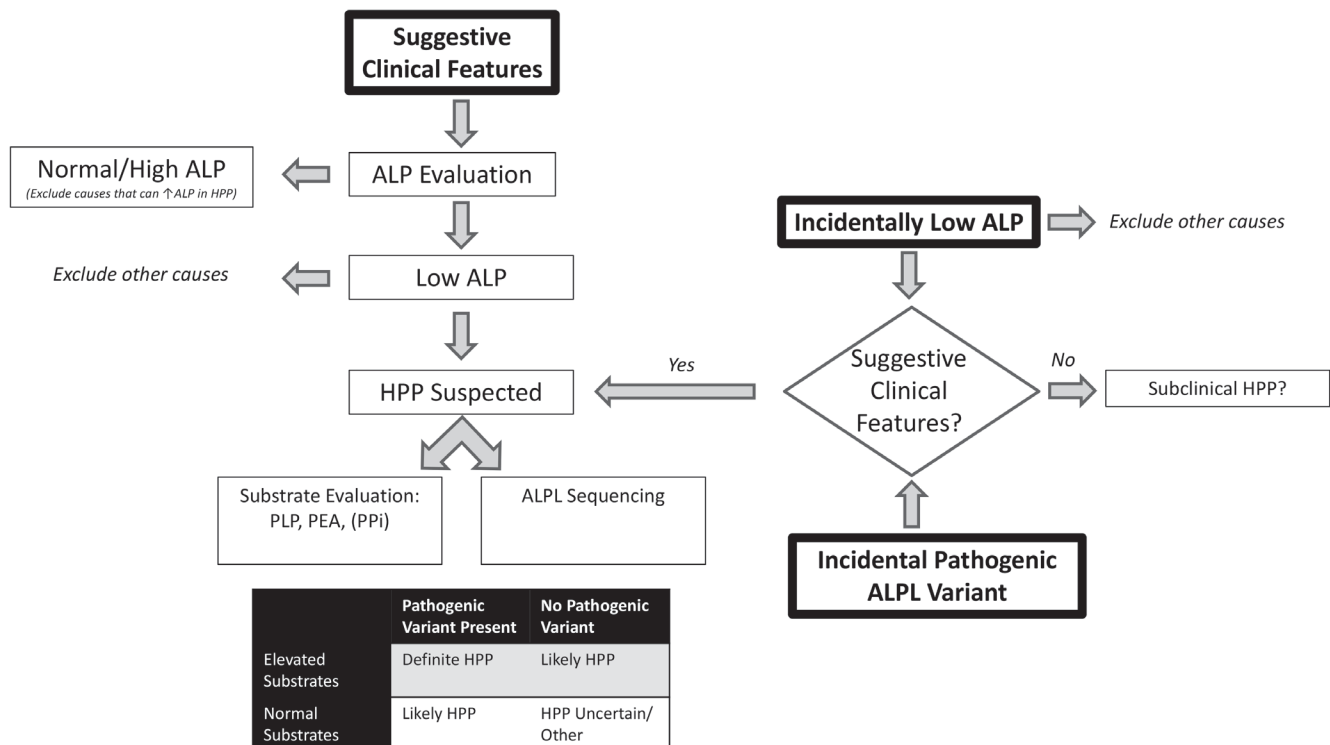
Which of the following is the most appropriate next step in this patient's management?

- A. Start intravenous zoledronic acid
- B. Start denosumab
- C. Start teriparatide
- D. Measure ALP isoenzymes
- E. Measure ALP substrates (PLP, PEA) and order genetic testing for *ALPL*

Answer: E) Measure ALP substrates (PLP, PEA) and order genetic testing for *ALPL*

This patient has multiple features suggestive of HPP, including persistently low-normal ALP, chronic musculoskeletal pain beginning in early

Figure. Diagnostic Pathways for HPP in Adults



Adults with HPP may enter the diagnostic pathway through suggestive clinical features, incidentally identified persistently low ALP, or incidental detection of a pathogenic *ALPL* variant. Persistently low or low-normal ALP, after exclusion of secondary causes, should prompt evaluation for HPP, recognizing that total ALP may be masked by non-TNSALP isoenzymes or transient increases in bone or liver ALP. Diagnostic confirmation relies on parallel, rather than sequential, assessment of physiologic TNSALP substrates (PLP, PEA, PPi when available) and *ALPL* sequencing. Diagnosis integrates clinical, biochemical, and genetic data rather than any single parameter.

[Color—Print (Color Gallery page CG7) or web & ePub editions]

adulthood, a previous stress fracture, dental disease, and a family history consistent with inherited low-ALP bone disease. There were no secondary causes of low ALP, such as malnutrition, hypothyroidism, hypoparathyroidism, multiple myeloma, celiac disease, glucocorticoid exposure, or antiresorptive therapy.^{2,23,40} The recommended next step is to confirm TNSALP dysfunction by measuring physiologic substrates (PLP, PEA) and to pursue *ALPL* testing, which are complementary rather than sequential (Answer E).^{13,14}

Borderline or intermittently normal total ALP does not exclude HPP. Total ALP can be “pushed” into the low-normal range by contributions from non-TNSALP isoenzymes (intestinal, placental, tumor-associated) and by transient increases in liver or bone ALP above a low baseline.^{14,23-26} In addition, routine ALP assays use artificial substrates under nonphysiological conditions and may fail to detect substrate-specific defects where hydrolysis of physiologic substrates is impaired despite preserved assay activity.^{17,27} Accordingly, assessment of physiologic substrates such as PLP and PEA is essential in patients with suggestive clinical features.

Antiresorptive therapy (Answers A and B) should be avoided until HPP is excluded, given the association with atypical femoral fractures and impaired fracture healing.^{15,16}

Teriparatide (Answer C) is not the first step before establishing the underlying metabolic bone disorder.^{13,14}

Measurement of ALP isoenzymes alone (Answer D) does not establish the diagnosis and should not delay definitive biochemical and genetic evaluation.^{13,14}

Case 1, Continued

Further evaluation demonstrates the following results:

Serum PLP = 44 µg/L (5-50 µg/L)

Urinary PEA = 57 nmol/mg creat (<48 nmol/mg creat)

Genetic testing identifies a heterozygous likely pathogenic variant in *ALPL*: c.1247G>A

(p.Gly416Asp). The Johannes Kepler University (JKU) *ALPL* Variant Portal catalogs this variant and reports functional data, including residual activity less than 5% and cotransfection assays demonstrating a dominant-negative effect.³⁰

Which of the following is the best interpretation of these findings?

- The patient does not have HPP because the PLP level is within the normal range
- The patient is a carrier of HPP because she has a heterozygous *ALPL* variant
- The mild urinary PEA elevation is predictive of mild disease severity
- The patient has HPP, and genotype and substrate levels do not reliably predict clinical severity
- The low residual enzymatic activity with a dominant-negative effect confirms severe childhood-onset HPP

Answer: D) The patient has HPP, and genotype and substrate levels do not reliably predict clinical severity

This patient meets adult HPP diagnostic criteria based on persistently borderline-low ALP, suggestive clinical features, and major diagnostic criteria, including elevation of a natural TNSALP substrate (urinary PEA) and identification of a likely pathogenic *ALPL* variant with demonstrated dominant-negative effects (Answer D).

The presence of a heterozygous likely pathogenic *ALPL* variant does not imply “carrier-only” status (Answer B). Many heterozygous pathogenic missense variants act through dominant-negative effects, reducing overall TNSALP activity when coexpressed with the wild-type protein.^{5,29} The JKU portal’s functional curation supports pathogenicity for this variant, but functional residual activity, substrate levels, and genotype correlate poorly with clinical severity in adults, so these results do not reliably predict age of onset, skeletal burden, or extraskeletal manifestations (Answer E).^{5,6,12,29,30,32,34} Population-based datasets reinforce this spectrum concept, showing that pathogenic or

likely pathogenic *ALPL* variants are more frequent than historically appreciated, but penetrance and phenotypic expressivity are variable.³¹⁻³⁴

Although elevation of TNSALP substrates supports the diagnosis of HPP, substrate testing has important limitations in adults. PLP can be normal in adult HPP due to preanalytic and biologic variability. PLP is light-sensitive and strongly influenced by dietary vitamin B₆ intake, supplementation, and kidney function, such that PLP levels may be normal or only intermittently elevated in adults with genetically confirmed HPP. Accordingly, a normal PLP level does not exclude HPP (Answer A). Elevated PEA supports enzyme dysfunction but does not grade severity; even mild elevations can be clinically meaningful (Answer C).^{14,28} For these reasons, expert consensus emphasizes that biochemical substrate testing and genetic testing are complementary and should be obtained together whenever feasible.^{13,14}

Case 2

A 63-year-old woman is referred for management of osteoporosis. She has a history of low-trauma fractures with delayed healing in her 20s and progressive daily musculoskeletal pain involving the hips, thighs, and lower legs that has worsened over the past decade and now limits daily activities.

Medical history includes hypertension, hyperlipidemia, and hypothyroidism. Medications include hydrochlorothiazide, amlodipine, rosuvastatin, and levothyroxine. She has never taken glucocorticoids or antiresorptive therapy. She has had persistently low ALP over the past 25 years (18-31 U/L [0.30-0.52 μ kat/L]) (reference range, 35-130 U/L [0.58-2.17 μ kat/L]).

Laboratory test results:

Calcium = 9.8 mg/dL (SI: 2.5 mmol/L)
 Phosphate = 4.3 mg/dL (SI: 1.4 mmol/L)
 PTH = 41 pg/mL (SI: 4.4 pmol/L)
 25-Hydroxyvitamin D = 42 ng/mL (SI: 104.8 nmol/L)
 TSH, normal
 Serum PLP = 97 μ g/L (<50 μ g/L)
 Urinary PEA = 23 nmol/mg creat (<48 nmol/mg creat)

DXA demonstrates:

Lumbar spine (L1-L3) T-score = -0.2 (Z-score +1.3)
 Total hip T-score = -1.7
 Femoral neck T-score = -2.7

Genetic testing for pathogenic *ALPL* variants is negative.

Which of the following is the best next step in this patient's evaluation and management?

- Obtain additional history regarding HPP manifestations in childhood
- Start alendronate
- Start denosumab
- Start PTH analogue therapy
- Start asfotase alfa

Answer: A) Obtain additional history regarding HPP manifestations in childhood

This patient has multiple features strongly suggestive of HPP, including persistently low ALP over decades, elevated serum PLP, chronic progressive musculoskeletal pain, delayed fracture healing, and a skeletal phenotype characterized by relatively preserved lumbar spine BMD with low hip BMD, which is typical of HPP rather than postmenopausal osteoporosis.^{10,15,41} Together, these findings satisfy 1 major criterion (elevated TNSALP substrate) and at least 2 minor criteria (poor fracture healing and chronic musculoskeletal pain) per the International Working Group diagnostic criteria, even in the absence of an identified pathogenic *ALPL* variant.^{12,13,38}

In the United States, asfotase alfa is FDA approved only for pediatric-onset HPP, and documentation of childhood manifestations has direct implications for treatment eligibility, insurance coverage, and access to enzyme replacement therapy.^{35-37,39} For this reason, the most appropriate next step in this patient's evaluation is to obtain a detailed childhood history (Answer A), including dental history, fracture patterns, physical limitations, and any available collateral information. While registry and real-world data suggest functional and skeletal

benefit in selected adults treated with asfotase alfa (Answer E), regulatory approval in the United States is limited to pediatric-onset HPP, making confirmation of childhood manifestations essential before treatment consideration.³⁹

Importantly, the distinction between “childhood-onset” and “adult-onset” HPP is biologically artificial. The underlying disease mechanism due to impaired TNSALP activity can persist and progress across the lifespan, and clinical severity reflects residual enzyme activity, dominant-negative effects, genetic modifiers, and cumulative mechanical stress, rather than the onset of features before or after age 18 years.⁵⁻⁸ Registry and biobank data demonstrate that many adults initially labeled as having “adult-onset” HPP are later found, on careful review, to have had subtle, unrecognized, or misattributed childhood manifestations, such as stress fractures, chronic limb pain, delayed fracture healing, or dental disease.^{7,8,13,32,34}

Antiresorptive therapy should generally be avoided in suspected HPP. Bisphosphonates (Answer B) and denosumab (Answer C) have been linked to atypical femoral fractures in adults with unrecognized HPP and do not address the underlying enzymatic defect.^{15,16}

Although anabolic agents (Answer D) have been used off-label in selected adults with HPP who lack access to enzyme replacement therapy, the benefits are variable and often transient, and treatment does not correct TNSALP deficiency.^{13,42-44}

Case 3

A 59-year-old woman is referred for evaluation of progressive muscle weakness, chronic musculoskeletal pain, and recurrent fractures. She reports difficulty rising from a chair and climbing stairs, as well as prolonged recovery after minimal exertion, with progressive limitation of daily activities over several years.

Her medical history includes multiple low-trauma fractures beginning in early adulthood, including bilateral foot fractures, a patellar fracture requiring open reduction and internal fixation complicated by hardware failure, a subsequent

low-trauma refracture, a periprosthetic fracture distal to knee arthroplasty, and a displaced comminuted shoulder fracture after a fall.

She recalls hip dysplasia, “growing pains,” frequent sprains, early tooth loss at age 4 years, multiple cavities during childhood, and dental extractions during adolescence. Family history is notable for a father who was edentulous by age 30 years with low ALP and hip and spine fractures; her adult son has low ALP but avoids medical care.

On physical examination, she has proximal muscle weakness. Functional testing shows a 5-times chair rise time of 27.5 s (normal <13 s) and a Timed Up and Go of 18.2 s (abnormal).

Laboratory studies reveal persistently low total ALP activity ranging from 16 to 25 U/L (0.27 to 0.42 μ kat/L) (reference range, 35-130 U/L [0.58-2.17 μ kat/L]); markedly elevated serum PLP (277 μ g/L [reference range, <50 μ g/L]); elevated urinary PEA (65 nmol/mg creat [reference range, <48 nmol/mg creat]); low liver ALP isoform; and normal calcium, phosphate, and PTH. DXA demonstrates preserved BMD. Genetic testing identifies a heterozygous pathogenic *ALPL* nonsense variant (c.303C>A; p.Tyr101*).

Which of the following best explains the expected skeletal and muscular response to asfotase alfa treatment in this patient?

- A. Significant increases in BMD
- B. Increase in the risk of atypical femoral fractures due to suppression of bone remodeling
- C. Improvement in muscle strength and physical function with minimal change in DXA
- D. Resolution of symptoms only if treatment had been initiated in childhood
- E. No clinical benefit in adults with normal baseline BMD

Answer: C) Improvement in muscle strength and physical function with minimal change in DXA

This patient has severe multisystem HPP with muscle and skeletal manifestations, supported by a lifelong history of fractures beginning in childhood, early tooth loss, persistently and

markedly low ALP, elevated TNSALP substrates (PLP and PEA), proximal muscle weakness, and profound functional impairment on objective testing (chair rise and Timed Up and Go). She also has a heterozygous pathogenic nonsense *ALPL* variant, which is sufficient to cause clinically significant disease due to loss of functional enzyme activity.^{13,30,38,45}

Despite an extensive fracture history, DXA demonstrates preserved or even above-average BMD, a well-described and misleading feature of adult hypophosphatasia.^{10,15,41} In HPP, impaired mineralization, accumulation of inorganic pyrophosphate, and altered bone material properties result in bone fragility that is not captured by areal BMD, particularly at the lumbar spine and hip. As such, DXA does not reliably reflect disease severity, fracture risk, or therapeutic response in HPP.^{10,15,41}

Muscle weakness, fatigue, exercise intolerance, and delayed recovery after exertion are increasingly recognized as core manifestations of adult HPP, independent of bone density.^{7,9,12,13,38} Experimental and translational studies demonstrate that TNSALP plays a role in muscle energetics, mitochondrial function, and phosphocreatine metabolism, providing a mechanistic basis for impaired muscle performance and fatigue in HPP.^{3,19-22} Clinically, these manifestations are best captured by functional assessments, such as chair rise time, Timed Up and Go, and gait speed, rather than DXA.

In adults with pediatric-onset HPP, treatment with asfotase alfa is consistently associated with improvements in physical function, mobility, pain, and quality of life, even when baseline bone density is normal or elevated.^{35-37,39,46-48} Registry data and longitudinal studies demonstrate improvements in walking distance, sit-to-stand performance, fatigue, and patient-reported outcomes, reflecting correction of systemic TNSALP deficiency rather than changes in areal BMD.^{35,37,39,46-48}

Accordingly, the expected therapeutic response in this patient is improvement in muscle strength, endurance, and functional performance, with little or no change in DXA measurements (Answer C).

This dissociation between clinical improvement and DXA response is characteristic of HPP in adults and reinforces the need to use functional and patient-centered endpoints, rather than BMD alone, to assess treatment benefit.^{37,39,49}

DXA changes with asfotase alfa in adults are typically modest or absent and generally do not reflect therapeutic benefit; functional improvement occurs largely independent of BMD changes (Answer A).⁴⁹

Asfotase alfa restores physiologic TNSALP activity and improves mineralization; it does not suppress bone remodeling and is not associated with an increased risk of atypical femoral fractures (Answer B).^{35,37,39,47}

While earlier treatment may prevent irreversible complications, adults with pediatric-onset HPP demonstrate meaningful improvements in pain, function, and mobility when treated later in life (Answer D).^{37,39,46,47,49}

Baseline DXA does not predict response. Adults with normal or elevated BMD frequently experience substantial functional and symptomatic improvement with enzyme replacement therapy (Answer E).^{35,39,47,49,50}

Key Learning Points

- HPP is a multisystem disease that is frequently misdiagnosed in adults.
- Diagnosis of HPP in adults requires an integrated assessment of phenotype, biochemistry, and genotype.
- DXA does not reliably assess fracture risk in HPP.
- Antiresorptive therapies may be harmful in HPP.
- Enzyme replacement therapy can improve function and quality of life in selected adults with HPP.

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CARDIOVASCULAR ENDOCRINOLOGY

Interpreting Aldosterone and Renin: Tricks of the Trade

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Consider the various factors affecting the interpretation of aldosterone and renin results.
- Identify which patients with primary aldosteronism (PA) could benefit from medical treatment and which might benefit from subtyping and adrenalectomy.
- Identify instances when patients might not require aldosterone-suppression testing or adrenal venous sampling (AVS).
- Describe challenges when interpreting aldosterone values during AVS and potential newer modalities for subtyping PA.

Significance of the Clinical Problem

Hypertension affects 1 in 3 adults worldwide and is a major cause of cardiovascular morbidity and mortality. Although most patients with hypertension have essential hypertension, studies have shown that 5% to 20% of patients with hypertension have PA. In these studies, PA was defined using traditional cutoffs for confirmatory testing.¹ However, more recent studies have shown that there is a spectrum of renin-independent aldosteronism, and the risk of cardiometabolic complications increases even

at aldosterone levels below the traditional cutoffs used to diagnose PA.² Hence, many more people are at risk of aldosterone-mediated cardiovascular disease (CVD) than currently recognized.

Compared with patients who have essential hypertension matched for age, sex, and blood pressure (BP), patients with PA are at a 2- to 3-fold higher risk of CVD and kidney failure,³ and they also experience a poorer quality of life. Hence, targeted treatment directed against aldosterone is necessary to ameliorate this risk. Diagnosing PA is also important because 30% to 60% of patients may have a unilateral adrenal pathology and could be candidates for curative unilateral adrenalectomy. Unilateral adrenalectomy completely cures PA in 90% to 97% of patients, and also improves or cures hypertension.⁴ Compared with patients managed with medical treatment, those treated with surgery have better outcomes.^{5,6} Furthermore, surgery reduces pill burden and improves quality of life.⁷ It is estimated that worldwide, less than 5% of all patients at high risk of PA are ever screened,⁸ and less than 0.1% of patients with unilateral PA undergo curative surgery.⁹

Practice Gaps

- Few patients worldwide are screened for PA, and even fewer are treated with mineralocorticoid receptor antagonist (MRA) therapy.

- Many patients with unilateral PA, a surgically curable form of PA, remain undiagnosed and are not offered potentially curative surgery.

Discussion

Screening and Diagnosis

The hallmark of PA is suppressed renin, with inappropriately elevated aldosterone. Case detection, or screening, is performed using the aldosterone-renin ratio (ARR). Patients with PA have high aldosterone levels and suppressed renin levels, resulting in an elevated ARR. Renin is secreted by the juxtaglomerular apparatus of the kidneys in response to baroreceptors. In volume- or salt-depleted states, renin is elevated, while in volume- or salt-overloaded states, renin is suppressed. Renin converts angiotensinogen to angiotensin I, which is in turn converted to angiotensin II by ACE. Aldosterone is chiefly regulated by angiotensin II, and also by potassium and ACTH. It is essential to always pair aldosterone measurements with serum potassium.

Numerous other factors can affect aldosterone and renin levels and must be considered when interpreting the ARR. Some patients with PA have hypokalemia, which can itself blunt aldosterone signals. Patients should receive adequate potassium supplementation to achieve normal potassium levels (≥ 3.5 mEq/L [≥ 3.5 mmol/L]). This is particularly important for patients with PA who have hypokalemia. Numerous classes of BP-lowering medications affect aldosterone levels. ACE inhibitors and angiotensin-receptor blockers (ARBs) lower aldosterone and raise renin levels, which can cause false-negative ARR results (*Table 1, following page*). Conversely, β -adrenergic blockers lower renin levels and, to a lesser extent, aldosterone levels, causing a false-positive ARR. Other factors, such as chronic kidney disease or aging, can increase aldosterone and lower renin levels, resulting in an elevated ARR. The latest iteration of the PA Endocrine Society guidelines recommends that screening tests may proceed while potentially interfering medications are still in use, with the results interpreted accordingly.

This aims to improve screening rates, which have been low. Patients with suppressed renin and inappropriate aldosterone signals despite being on ACE inhibitors or ARBs, for example, are considered to have a positive screening test for PA.

Confirmatory Testing (Aldosterone-Suppression Test)

After a positive screening ARR, patients may be recommended to undergo confirmatory testing or aldosterone-suppression testing. The latest Endocrine Society guidelines recommend that patients with a low probability of lateralizing PA proceed directly to a trial of MRA therapy rather than confirmatory tests. Similar to previous guidelines, those with a high probability of lateralizing PA (spontaneous hypokalemia, suppressed renin, and plasma aldosterone concentration (PAC) above 20 ng/dL [>555 pmol/L]) may proceed directly to imaging and subtyping studies without a suppression test. Therefore, only patients with an intermediate likelihood of lateralizing PA are advised to undergo aldosterone-suppression testing. Failure to suppress aldosterone to prespecified thresholds is consistent with the diagnosis of PA. Current aldosterone-suppression tests include (1) intravenous seated saline-suppression test (SST), (2) oral salt loading, (3) captopril challenge test, and (4) fludrocortisone-suppression test.

Subtyping of PA

Adrenal Venous Sampling

Identifying the abnormal adrenal gland(s) is crucial in PA and is referred to as subtyping. CT of the adrenals is generally not adequately accurate to determine the PA subtype in most cases. While CT may detect adrenal adenomas, it can miss aldosterone-producing adenomas (APAs) smaller than 8 mm in diameter. Additionally, 5% to 8% of the normal population harbors adrenal nodules, which may be nonfunctional, and the prevalence increases with age. AVS involves selective cannulation of the adrenal veins and identification of the site(s) of aldosterone excess

based on biochemical rather than radiologic findings and has conventionally been regarded as the gold standard in PA subtyping. Exceptions are

made for young patients (<35 years) with overt PA, a unilateral adrenal adenoma, and a normal contralateral adrenal gland who may bypass AVS

Table 1. Factors That May Cause False-Positive and -Negative ARR Results¹⁰⁻¹³

Factors	Effect on plasma aldosterone level	Effect on plasma renin levels	Effect on ARR	Implication
Potassium status				
Hypokalemia	↓	↔, ↑	↓	False negative
Hyperkalemia	↑	↔, ↓	↑	False positive
Dietary sodium				
Sodium restriction	↑	↑↑	↓	False negative
Sodium loading	↓	↓↓	↑	False positive
Medications				
Potassium-wasting diuretics (eg, furosemide)	↔, ↑	↑↑	↓	False negative
Potassium-sparing diuretics (eg, amiloride, triamterene)	↑	↑↑	↓	
Mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone, finerenone)	↔, ↑	↑↑	↓	
SGLT-2 inhibitors	↔	↑	↓	
ACE inhibitors	↓	↑↑	↓	
ARBs	↓	↑↑	↓	
Dihydropyridine calcium-channel blockers	↔, ↑	↑	↓	False positive
β-Adrenergic blockers	↓	↓↓	↑	
Central agonists (eg, clonidine, methyldopa)	↓	↓↓	↑	
Nonsteroidal anti-inflammatory drugs	↓	↓↓	↑	
Oral estrogen-containing pill ^a	↑	↓	↑	
Drospirenone	↑	↑	↔, ↑	-
Others				
Renovascular hypertension	↑	↑↑	↓	False negative
Pregnancy	↑	↑↑	↓	
Aging	↓	↓↓	↑	False positive
Chronic kidney disease	↑	↑, ↔, ↓	↑	

Legend: ↑ increased, ↔ unchanged, ↓ decreased

^a Estrogen stimulates the hepatic production of angiotensinogen, a renin substrate, leading to increased plasma renin activity. This, however, results in a reduced direct renin concentration.

and proceed directly to adrenalectomy. This is because nonfunctional adrenal incidentalomas are uncommon in young patients. For most patients with PA, AVS remains the standard of care for those seeking surgical cure.¹⁰ Nevertheless, AVS is invasive, technically challenging, and frequently yields inconclusive result.¹⁴ The necessary infrastructure and technical expertise are also not available in various regions worldwide.¹⁵

Treatment of PA

Laparoscopic unilateral adrenalectomy offers an opportunity to cure PA and improve or cure hypertension in patients with unilateral PA. Patients with bilateral PA or those not seeking surgical treatment should be prescribed medical therapy. Medical treatment with MRA, such as spironolactone, effectively lowers blood pressure, corrects hypokalemia, and reduces the risk of CVD. However, spironolactone may cause antiandrogenic adverse effects, particularly in men, such as gynecomastia and low libido, while women may experience menstrual irregularities.¹⁶ Spironolactone is also contraindicated during pregnancy. For patients experiencing adverse effects due to spironolactone, alternatives include eplerenone (only FDA approved for hypertension) or amiloride, an epithelial sodium-channel inhibitor. Importantly, adequate dosing is required to achieve full MR blockade. Goals of MRA therapy include normokalemia (if hypokalemia was previously present, preferably with high-normal potassium levels), normal BP, and unsuppressed renin levels.¹⁷

What's New?

Expanding Spectrum of PA or Renin-Independent Hyperaldosteronism

There have been several updates in the recent 2025 Endocrine Society guidelines. First, ***universal screening for all patients with hypertension*** is now recommended. Second, there is less emphasis on discontinuing interfering antihypertensive medications. Instead, patients can be tested while on interfering medications, and ARR results

should be interpreted in the context of those medications. Third, patients not considering surgical treatment can proceed directly to medical treatment, without undergoing aldosterone-suppression testing.

There are several reasons behind these changes. Although studies over the last 25 years have shown that PA affects 5% to 20% of all patients with hypertension, PA screening rates remain abysmal worldwide: fewer than 1% of patients are ever tested for PA, and even in patient subgroups at high risk for PA (eg, those with hypertension and hypokalemia, and resistant hypertension), screening rates remain less than 5% to 10%. Patients with PA often experience prolonged periods of hypokalemia before testing.¹⁸ To reduce screening barriers, changes in antihypertensive agents are not required for all patients, and greater allowance is made for interpreting the ARR in the context of interfering medications. Since most patients with hypertension are managed by primary care physicians, simplifying the screening process is expected to increase overall screening rates.

Renin-independent aldosteronism is now recognized as a spectrum of pathology,² and patients with PA represent only the highest end of this spectrum, defined by arbitrary cutoffs. Hence, many more individuals are exposed to the effects of hyperaldosteronism through increased activation at the MR and will benefit from treatment with MRA. Even patients with suppressed aldosterone after aldosterone-suppression testing may respond well to MRA.¹⁹ Thus, instead of mandating confirmatory testing, which may not be widely available,¹⁵ an MRA trial is recommended. This is also a suggested approach if the likelihood of unilateral PA is low (eg, marginally elevated PAC and normal serum potassium).

Pearls and Pitfalls in PA Screening

When interpreting the screening ARR, apart from the factors mentioned above, there are 2 other important considerations: (1) the likelihood

of unilateral PA and (2) biological variability (intraindividual) and assay variability.

Likelihood of Unilateral PA

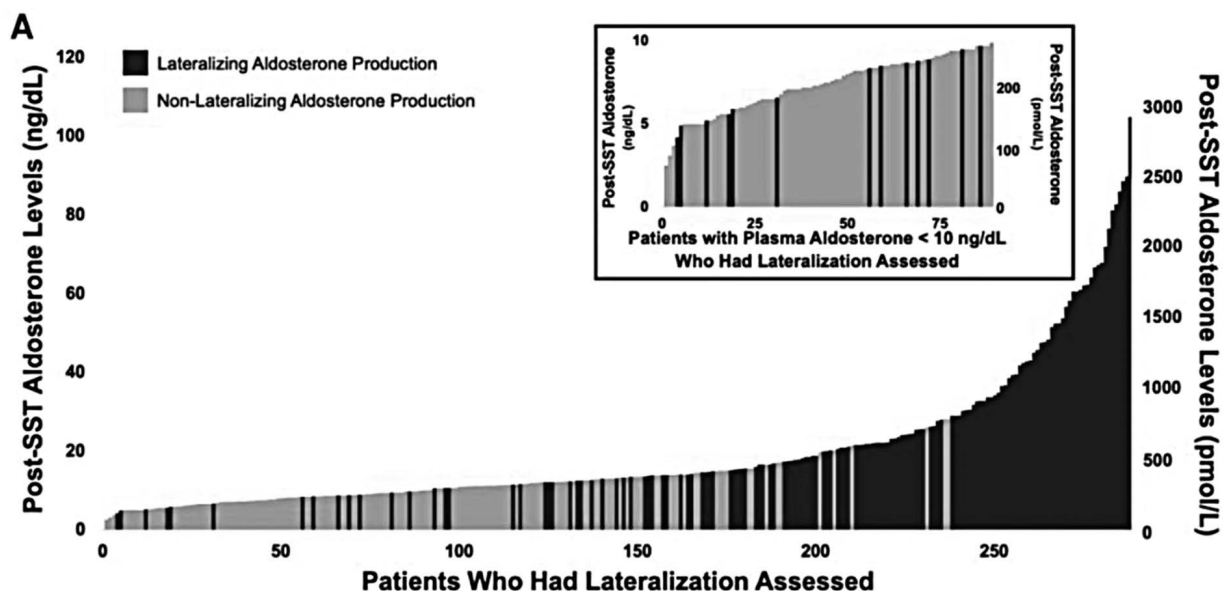
Since only patients with unilateral PA can be offered unilateral adrenalectomy, the next important factors to consider are (1) whether the patient is interested in surgical treatment, and (2) the likelihood of unilateral PA. Various prediction models developed have shown that higher baseline aldosterone levels and more severe hypokalemia increase the likelihood of unilateral PA.^{20–22} Generally, patients with a more severe PA phenotype (higher plasma aldosterone, lower serum potassium, and more severe hypertension) are more likely to have unilateral PA. Suppression tests are also useful, with post-SST aldosterone levels predicting the likelihood of unilateral PA. As shown in this study (*Figure 1*), patients with higher postsuppression aldosterone levels were more likely to have lateralization on AVS (unilateral PA) than those with lower postsuppression levels. However, as many as 15% of patients with postsuppression aldosterone levels less than

10 ng/dL (<277 pmol/L) had AVS lateralization. Therefore, the decision to pursue subtyping should be individualized, taking into account each patient's intent for surgical cure.

Biological and Assay Variability

There is inherent variability in aldosterone and renin measurements due to biological (intraindividual) factors and assay variability. Aldosterone secretion is variable, with intraday and interday fluctuations.²⁴ As aldosterone is also regulated by ACTH, its levels are generally higher in the morning than in the afternoon. However, recent studies have shown that even in patients with surgically cured unilateral PA, aldosterone levels may be much lower, and even in the normal range on some days.²⁵ Hence, in patients with a high pretest probability of PA, such as those with unexplained hypokalemia and hypertension, it may be worthwhile to repeat the ARR if the first test is negative. Assay variability refers to differences in test results when the same biospecimen is measured repeatedly with the same assay. This variability is approximately 10%

Figure 1. Lateralization of Aldosterone Production and Treatment Decisions as a Function of SST



Lateralization of aldosterone production. Lateralization was assessed via AVS or imaging for a unilateral adrenal mass in patients with overt PA and hypokalemia; 143 of 288 patients (49%) were determined to have lateralizing PA. The inset depicts a magnified view of only those participants who had a post-SST aldosterone value less than 10 ng/dL (<277 pmol/L), wherein 13 of 89 patients (15%) had lateralizing PA (15%). Reprinted from Parksook WW et al. *J Clin Endocrinol Metab*, 2024; 109(9): 2220–2232. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.²³

[Color—Print (Color Gallery page CG8) or web & ePub editions]

or lower regardless of whether immunoassays or liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays are used.

Increased Use of LC-MS/MS Assays

The 2025 Endocrine Society guidelines recommend different thresholds for measuring aldosterone by immunoassays or LC-MS/MS. Renin may be measured by plasma renin activity (PRA) or direct renin concentration (DRC). Plasma renin activity is measured by the amount of angiotensin I generated (bioassay), while DRC directly measures the quantity of renin in the serum. Angiotensin I and aldosterone can be measured by immunoassay, radioimmunoassay, or LC-MS/MS.

LC-MS/MS offers much greater specificity for measuring analytes. Hence, aldosterone levels measured by LC-MS/MS may be 20% to 80% lower than those measured by immunoassays.^{26,27} The Endocrine Society recommends using a 25% lower cutoff when interpreting LC-MS/MS results.¹⁰ Circulating aldosterone levels are 1000 times lower than cortisol levels, and cross-reactivity with cortisol or other analytes can cause falsely elevated aldosterone readings. Aldosterone measured by immunoassay is less accurate at low levels, particularly at approximately 7.2 ng/dL and below (≤ 200 pmol/L). This is critically close to the diagnostic threshold used for PA. In one study, aldosterone levels measured by immunoassay were 50% to 80% higher than those measured by LC-MS/MS. Furthermore, almost all patients with postsuppression positive results on immunoassay but negative results on LC-MS/MS had bilateral PA, suggesting that immunoassay results may lead to false-positive diagnoses and unnecessary AVS procedures.²⁷ Screening with ARR relies on high aldosterone and low renin levels, which inflate the ratio and improve sensitivity. Traditionally, ARR using PRA has been more widely espoused and studied,²⁸ while ARR using DRC may yield false-negative results. Ultimately, the choice of assays used in practice often depends on their availability.

Molecular Imaging

Molecular imaging has routinely been used to localize endocrine tumors, such as radio-labeled somatostatin analogue imaging for paragangliomas. Both ^{11}C -metomidate PET-CT and ^{68}Ga -pentixafor have been used in clinical trials to subtype PA. Metomidate (MTO) inhibits CYP11B1 (cortisol synthesis) and CYP11B2 (aldosterone synthesis) and can be ^{11}C -labeled for PET imaging. Patients are prescribed dexamethasone before imaging to enhance MTO's selectivity for CYP11B2. The largest trial to date, the MATCH study, demonstrated that ^{11}C -MTO PET-CT was noninferior to AVS.²⁹ Importantly, some patients with unilateral PA without lateralization on AVS had clear lateralization on ^{11}C -MTO PET-CT. These patients achieved complete biochemical remission after unilateral adrenalectomy. If available, this noninvasive subtyping modality could also serve as a first-line subtyping tool, obviating the need for an invasive test if the result is positive.³⁰ It may also be used if AVS is unsuccessful or unavailable. However, current radiotracers for PA imaging are still not widely available.

Hybrid Hormones and Steroid Profiling

Due to the limitations of aldosterone and renin outlined above, hybrid hormones and steroid profiling offer strong complements to the ARR. Up to 95% of APAs harbor a somatic pathogenic variant that drives autonomous aldosterone release.³¹ Pathogenic variants in the *KCNJ5* gene are the most common somatic variants in APAs measuring 1 cm or larger and appear to be more prevalent among people of Asian ancestry. Patients with a *KCNJ5*-variant APA appear to have the best postsurgery prognosis, with the greatest likelihood of complete cure of hypertension.²⁹ Importantly, those with a *KCNJ5*-variant APA often have high levels of hybrid hormones (18-oxocortisol and 18-hydroxycortisol), with 18-oxocortisol exceeding 6.1 ng/dL.³² Therefore, patients with a visible adenoma on CT imaging may be offered surgery if their hybrid hormone levels are markedly elevated. This approach needs

further validation in prospective trials (Figure 2). In addition to these hybrid hormones, steroid profiling combined with machine-learning artificial intelligence models has proven to be accurate as both a screening test for PA and for subtyping unilateral PA.³³ This may, in the future, be superior to relying on a single hormone measurement (aldosterone) for diagnosing PA.

Clinical Case Vignettes

Case 1

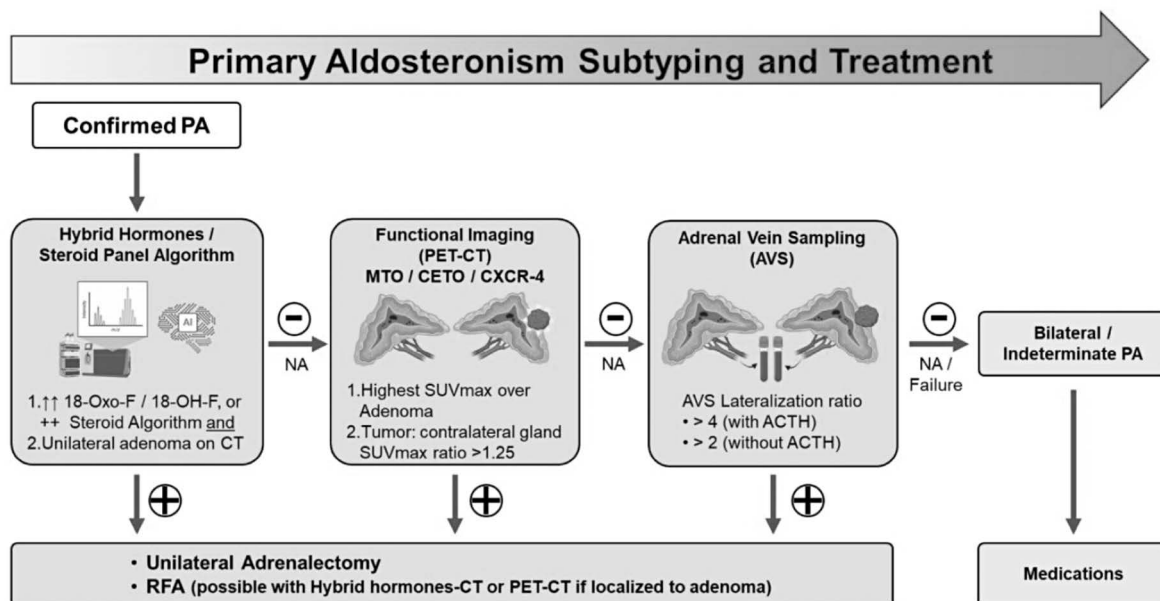
A 63-year-old man with a 20-year history of hypertension and a 10-year history of type 2 diabetes and hyperlipidemia is referred for bilateral adrenal incidentalomas. He was seen by a urologist for an episode of urinary tract infection. CT intravenous pyelography showed a 2.2×1.8 -cm nodule in the medial limb of the right adrenal gland (precontrast attenuation, 5 Hounsfield units [HU]) and a 2.4-cm nodule in the medial limb of the left adrenal gland (precontrast attenuation, 14 HU). His BP is uncontrolled at 146/91 mm Hg

despite being on 3 antihypertensive medications: valsartan, 160 mg daily; nifedipine, 60 mg daily; and hydrochlorothiazide, 25 mg daily. Other medications include aspirin, 100 mg daily; atorvastatin, 10 mg daily; and metformin, 2000 mg daily.

His baseline laboratory test results:

Baseline creatinine = 0.70 mg/dL (0.74-1.41 mg/dL)
(SI: 62 μ mol/L [65-125 μ mol/L])
Urinary albumin-to-creatinine ratio = 306 mg/g
(0-30 mg/g)
PAC = 12 ng/dL (SI: 333 pmol/L)
PRA = <0.4 ng/mL per h
ARR = 30
Serum potassium = 3.8 mEq/L (SI: 3.8 mmol/L)
Urinary metanephrine = 172.6 μ g/24 h
(78.9-295.9 μ g/24 h) (SI: 875 nmol/d
[400-1500 nmol/d])
Urinary normetanephrine = 327.8 μ g/24 h
(109.9-348.0 μ g/24 h) (SI: 1790 nmol/d
[600-1900 nmol/d])
Cortisol after 1-mg overnight dexamethasone
suppression = 1.3 μ g/dL (SI: 35 nmol/L)

Figure 2. Proposed Future Algorithm for Subtyping PA



Abbreviations: NA, not available; SUVmax, maximum standardized uptake value. Current data suggest that each subtype test is highly specific. Hence, this algorithm recommends using them sequentially, from least to most invasive: hybrid hormone/steroid panel algorithm, molecular imaging, and AVS. *Clear lateralization for ^{11}C -MTO PET-CT uses an SUV_{max} ratio of greater than 1.25; thresholds with other radiotracers would differ. Reprinted from Ada E D Teo et al. *J Clin Endocrinol Metab*, 2025; 110(12): 3559-3568. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.³⁰

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The patient is not interested in pursuing surgical treatment for hypertension.

Which of the following is the best next step?

- A. Remove interfering antihypertensive medications before repeating ARR
- B. Remove interfering antihypertensive medications before performing aldosterone-suppression testing
- C. Proceed directly to aldosterone-suppression testing
- D. Start medical treatment with MRA

Answer: D) Start medical treatment with MRA

This patient has a positive ARR of 30, with both elevated aldosterone and suppressed renin levels despite being on medications (an ARB and thiazidelike diuretic). Both medications can lower the ARR, while the ARB would also lower the PAC. Hence, there is no need to stop these medications for repeat ARR testing or perform aldosterone-suppression testing. In a patient who is not keen on surgery, further confirmatory testing does not affect clinical decisions, as MRA treatment is recommended. Consequently, we can omit aldosterone-suppression testing altogether and proceed directly to treatment.

Patients who are not surgical candidates or not interested in surgery can skip confirmatory testing. Reasons may include comorbidities such as CVD, stroke, or chronic kidney disease, which render them poor surgical candidates. Patients may also prefer lifelong medications to surgery. Spironolactone is the first-line medical option in most patients, as it is cheap and effective. However, its antiandrogenic adverse effects are more troubling for men, particularly at higher doses. It is also contraindicated in pregnancy. In postmenopausal women, spironolactone is generally well tolerated, and this group of patients may prefer first-line medical treatment over surgery. In patients with bilateral macronodular adrenal hyperplasia, PA is typically bilateral; further confirmatory testing or subtyping is unnecessary.

After starting spironolactone, the patient's BP improved to 119/81 mm Hg. His albuminuria also resolved (6 mg/g), while his creatinine increased from 0.70 to 1.19 mg/dL (62 to 106 μ mol/L).

Case 1, Continued

Which of the following is the best next step?

- A. Stop spironolactone
- B. Reduce the dosage of spironolactone to 12.5 mg daily
- C. Switch to eplerenone
- D. Continue the current dosage of spironolactone, 25 mg daily, and monitor

Answer: D) Continue the current dosage of spironolactone, 25 mg daily, and monitor

Chronic aldosterone excess leads to increased sodium reabsorption, increased renal perfusion pressure, and glomerular hyperfiltration. In addition, hyperaldosteronism leads to increased renal and cardiac fibrosis. Hence, it is important for patients with PA to be treated with aldosterone-targeted therapy. Treatment reverses glomerular hyperfiltration and reduces proteinuria, and there may be a transient elevation in serum creatinine levels. This is also seen frequently in patients with diabetes treated with ACE inhibitors. Therefore, in patients with a 20% to 30% increase in serum creatinine after starting MRA therapy, we recommend continued close monitoring at the same dosage. In most patients with PA, the serum creatinine level stabilizes or even falls subsequently. This patient's subsequent creatinine level has remained stable at 0.89 mg/dL (79 μ mol/L) while on the same spironolactone dosage 4 years later. Switching to eplerenone or amiloride could be considered for patients experiencing antiandrogenic adverse effects of spironolactone.

Case 2

A 55-year-old man has a history of hypertension since age 35 years and is currently on 3 antihypertensive medications. He has had hypokalemia since age 45 years, but this had

not been previously evaluated. He has minor coronary artery disease diagnosed on CT coronary angiography. His cardiac MRI shows an ejection fraction of 70% and severe concentric left ventricular hypertrophy.

Baseline laboratory values (by LC-MS/MS assay) while on valsartan, atenolol, and nifedipine:

PAC = 25 ng/dL (SI: 694 pmol/L)
 PRA = 1.8 ng/mL per h
 ARR = 13.8
 Corresponding serum potassium = 4.1 mEq/L
 (SI: 4.1 mmol/L) while on potassium chloride,
 1.2 g daily

His regimen is switched to hydralazine and prazosin, and subsequent repeat ARR is positive. A seated intravenous SST is performed, with a postsaline infusion PAC less than 4 ng/dL (<111 pmol/L) (*Table 2*). Another repeat ARR is positive, with a markedly elevated PAC. He would like to pursue unilateral adrenalectomy if indicated.

Which of the following is the best next step?

- A. Send aldosterone and renin to another lab using LC-MS/MS
- B. Repeat aldosterone-suppression testing
- C. Offer medical therapy with MRA
- D. Proceed directly to AVS

Answer: D) Proceed directly to AVS

This patient has a history of longstanding hypertension and hypokalemia, and the pretest probability of PA (and unilateral PA) is high. His initial ARR was negative, which can be confounded by the use of ACE inhibitors and diuretics. Unusually, his PRA was not suppressed despite taking a β -adrenergic blocker. In view of a negative ARR, removal of these interfering medications was warranted before repeating the ARR. Although ARR was subsequently positive, he had a negative result on an aldosterone-suppression test. However, a repeat ARR thereafter showed markedly elevated aldosterone levels, confirming the diagnosis of PA and obviating the requirement for aldosterone-suppression testing: overtly high aldosterone levels (PAC >20 ng/dL [>554.8 pmol/L] on immunoassay, or >15 ng/dL [>416.1 pmol/L] on LC-MS/MS), suppressed renin levels, and spontaneous hypokalemia.

There are several learning points from this case. First, it illustrates interday variability in aldosterone levels among patients with PA. Despite the consistent use of similar noninterfering medications and similar potassium levels, the ARR may fluctuate significantly from day to day. In this patient, ARR #3 was more than twice that of ARR #2. Second, samples for baseline laboratory assessment should be collected before the start of aldosterone-suppression testing. This provides a useful opportunity to

Table 2. Case 2 Patient's ARR and SST Results

	4/30/20 ARR #1	7/2/20 ARR #2	4/1/21 (pre-SST)	4/1/21 (post-SST)	2/9/21 ARR #3
PAC	25.0 ng/dL (SI: 694 pmol/L)	13.0 ng/dL (SI: 361 pmol/L)	11.0 ng/dL (SI: 305 pmol/L)	<4.0 ng/dL (SI: 111 pmol/L)	31.0 ng/dL (SI: 860 pmol/L)
PRA	1.8 ng/mL per h	<0.6 ng/mL per h	<0.6 ng/mL per h	<0.6 ng/mL per h	<0.6 ng/mL per h
ARR	13.8	21.7	18.3	6.7	51.7
Potassium	4.1 mEq/L (SI: 4.1 mmol/L)	4.2 mEq/L (SI: 4.2 mmol/L)	3.1 mEq/L (SI: 3.1 mmol/L)	3.7 mEq/L (SI: 3.7 mmol/L)	3.7 mEq/L (SI: 3.7 mmol/L)
Antihypertensive medications and potassium	KCL, 1.2 g daily Atenolol Valsartan Nifedipine	KCL, 1.2 g daily Prazosin Hydralazine Nifedipine			

reassess ARR, as it is often performed early in the morning in a seated position, before saline or captopril challenge. Third, patients presenting with hypokalemia have a high pretest probability of PA, particularly unilateral PA. Hence, if the initial ARR is negative, it is worthwhile to repeat the ARR and consider withdrawing interfering medications. Fourth, in patients with suspected PA but elevated PRA levels, it is important to ensure adequate dietary sodium intake, as a low-sodium diet may cause a false-negative ARR.

Finally, instead of treating each pair of aldosterone and renin results as definitive and categorizing patients dichotomously (ie, PA vs not PA, or bilateral PA vs unilateral PA), it is more useful to consider all the information and assess the likelihood of unilateral PA. The aldosterone-suppression test offers additional insight into the likelihood of unilateral PA, which in this patient was low, as aldosterone was fully suppressible. Nonetheless, this could be affected, in part, by biological or assay variability. Conversely, this patient had numerous factors suggestive of unilateral PA (spontaneous hypokalemia, very high aldosterone levels on one occasion). Taken together, he still had a fair possibility of unilateral PA. Since he was keen to pursue surgery if unilateral PA was confirmed, further subtyping was warranted.

Case 2, Continued

CT showed nodular adrenal glands bilaterally, suggestive of adrenal hyperplasia, and he proceeded with AVS with continuous cosyntropin stimulation (*Table 3*).

Cortisol levels in both adrenal veins were at least 5 times higher than in the inferior vena cava, confirming successful cannulation. The aldosterone-to-cortisol ratio in the right adrenal vein was 9.7 times greater (more than 4 times) than the left aldosterone-to-cortisol ratio, consistent with lateralization to the right adrenal gland. There was also contralateral suppression of the left gland, with the aldosterone-to-cortisol ratio of the left adrenal vein lower than that of the inferior vena cava. The patient proceeded with right adrenalectomy. After surgery, his BP improved to 103/65 mm Hg while on the same number of antihypertensive medications, and he achieved complete biochemical success: PAC = 4.0 ng/dL (111 pmol/L), PRA = 0.6 ng/mL per h, and normal potassium without supplementation.

Case 3

A 49-year-old woman presents with a 10-year history of hypertension.

Table 3. Case 2 Patient's AVS Results

Measurement	Right adrenal vein	Inferior vena cava	Left adrenal vein
PAC	1400 ng/dL (SI: 38,836 pmol/L)	42 ng/dL (SI: 1165 pmol/L)	73 ng/dL (SI: 2025 pmol/L)
Cortisol	491 µg/dL (SI: 13,543 nmol/L)	24 µg/dL (SI: 657 nmol/L)	244 µg/dL (SI: 6726 nmol/L)
Cortisol gradient	20.6	NA	10.2
PRA	NA	<0.6 ng/mL per h	NA
Potassium	NA	3.8 mEq/L (SI: 3.8 mmol/L)	NA
Aldosterone-to-cortisol ratio	2.9	1.8	0.30

Lateralization ratio to the right: $2.9/0.3 = 9.7$

Contralateral suppression of the left: $0.3/1.8 = 0.2$

Initial laboratory results while on hydralazine and verapamil:

PAC = 33.8 ng/dL (SI: 938 pmol/L)
 PRA = 1.7 ng/mL per h
 Corresponding potassium = 4.1 mEq/L
 (SI: 4.1 mmol/L)

After changing medications, she proceeds with an intravenous SST, with a post-SST suppression PAC value of 24.5 ng/dL (680 pmol/L), consistent with the diagnosis of PA (Table 4).

CT shows an 8-mm nodule in the right adrenal gland, and she proceeds with AVS with cosyntropin stimulation (Table 5).

What do the AVS results show, and how would you proceed?

- Bilateral PA; start medical treatment with MRA
- Inconclusive AVS with failed cannulation; repeat AVS
- Inconclusive AVS; consider further subtyping options like molecular imaging (PET-CT) or hybrid hormones if available
- Clear lateralization to the right; offer right laparoscopic adrenalectomy

Answer: C) Inconclusive AVS; consider further subtyping options like molecular imaging (PET-CT) or hybrid hormones if available

Table 4. Case 3 Patient's ARR and SST Results

	8/7/17 ARR #1	9/26/18 Pre-SST ARR #2	9/26/18 Post-SST
PAC	33.8 ng/dL (SI: 938 pmol/L)	39.0 ng/dL (SI: 10.82 pmol/L)	24.5 ng/dL (SI: 680 pmol/L)
PRA	1.7 ng/mL per h	<0.6 ng/mL per h	0.9 ng/mL per h
ARR	19.9	65	27.2
Potassium	4.1 mEq/L (SI: 4.1 mmol/L)	3.6 mEq/L (SI: 3.6 mmol/L)	3.8 mEq/L (SI: 3.8 mmol/L)
Antihypertensive medications and potassium	Losartan, 50 mg once daily Amlodipine, 10 mg once daily	Hydralazine, 75 mg 3 times daily Verapamil, 80 mg 3 times daily	

Table 5. Case 3 Patient's AVS Results

Measurement	Right adrenal vein	Inferior vena cava	Left adrenal vein
PAC	2729 ng/dL (SI: 75,702 pmol/L)	106 ng/dL (SI: 2940 pmol/L)	393 ng/dL (SI: 10,902 pmol/L)
Cortisol	529.9 µg/dL (SI: 14,618 nmol/L)	42.3 µg/dL (SI: 1167 nmol/L)	234.8 µg/dL (SI: 6479 nmol/L)
Cortisol gradient	12.5	NA	5.6
PRA	NA	1.5 ng/mL per h	NA
Potassium	NA	3.6 mEq/L (SI: 3.6 mmol/L)	NA
Aldosterone-to-cortisol ratio	5.17	2.52	1.68

Lateralization ratio to the right: $5.17/1.68 = 3.1$

Contralateral suppression of left: $1.68/2.52 = 0.7$

This patient's AVS was successful because the cortisol gradients were both at least 5 times higher than the peripheral inferior vena cava cortisol level. A threshold of 5 is used when AVS is performed with cosyntropin, and a lower threshold (2 or 3) is used when AVS is performed without cosyntropin. A lateralization ratio greater than 4 times is consistent with unilateral PA, and a lateralization ratio less than 3 times is consistent with bilateral PA. A lateralization ratio of 3 to 4 times is indeterminate, as some patients may have unilateral PA and benefit from unilateral adrenalectomy. If no further options are available, then offering adrenalectomy may be reasonable if the patient is aware of the possibility of persistence of PA. Even in patients with clear lateralization on AVS with ratios 4 times or even 10 times or higher, there remains a 2% to 5% risk of persistent PA after surgery, attributed to asymmetric, bilateral PA.

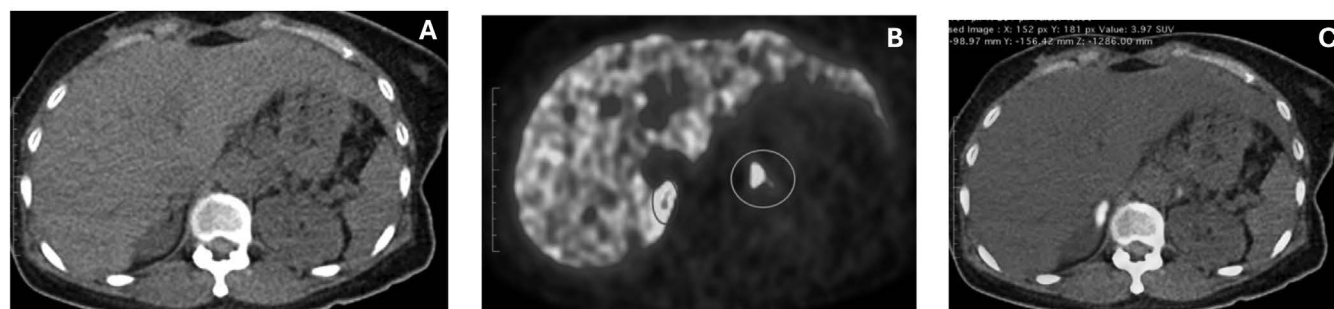
If available, molecular functioning could be performed. This patient underwent ^{11}C -metomidate PET-CT, demonstrating intense uptake in the right adrenal nodule, with a maximal standardized uptake value (SUV_{max}) of 47.3, compared with a left adrenal SUV_{max} of 24.2, yielding a ratio of 1.95 (above the threshold of 1.25) (Figure 3). This was consistent with lateralization to the right adrenal gland, specifically localization to the right adrenal nodule. In addition, her baseline hybrid hormones were both elevated: 18-oxocortisol = 10.6 ng/dL (above the

threshold of 6.1 ng/dL) and 18-hydroxycortisol = 142.2 ng/dL. She proceeded with right unilateral adrenalectomy. CYP11B2 immunohistochemistry staining performed in the resected gland showed an 11-mm APA, with predominantly zona-fasciculata cells. One year after surgery, hypertension was completely cured, and she achieved complete biochemical success: PAC = 4.0 ng/dL (111 pmol/L), PRA = 3.1 ng/mL per h, and serum potassium = 4.0 mEq/L (4.0 mmol/L).

Key Learning Points

- PA is common and linked to increased cardiovascular complications but remains underdiagnosed worldwide.
- To improve case detection, all patients with hypertension should be screened for PA, regardless of their medications, and results should be interpreted accordingly.
- Patients with a low likelihood of unilateral PA, who are not suitable candidates for surgery or are not interested in surgical options, do not need aldosterone-suppression testing and should be offered MRA therapy.
- Patients with PA who have a moderate or high likelihood of unilateral disease and are interested in surgery should undergo subtyping with AVS. Newer subtype techniques, including molecular imaging and hybrid hormones, may be considered if available.

Figure 3. Case 3 Patient's Imaging



^{11}C -Metomidate PET-CT with Panel A, CT showing a right-sided 8-mm adrenal nodule; Panel B, highly PET-avid on PET with SUV_{max} of 47.3 compared with the left gland with an SUV_{max} of 24.2; Panel C, the fused images showing that the highest PET uptake is over the adrenal adenoma.

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Beyond Statin Therapy for Hypercholesterolemia in Adults

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the high burden of residual cardiovascular risk even after institution of appropriate statin therapy for primary and secondary prevention.
- Explain the mechanisms of action of nonstatin drugs used to lower cholesterol levels, including ezetimibe, bempedoic acid, and PCSK9 inhibitors.
- Determine the role of additional nonstatin therapies in patients with hypercholesterolemia, based on available clinical trial data.

Significance of the Clinical Problem

Despite many scientific advances and societal changes, cardiovascular disease (CVD) remains the leading cause of death in both developed and developing countries. More than half of US death certificates mention CVD, and over one-third list it as the underlying cause of death. However, it is encouraging that over the past few decades, the incidence of death due to coronary heart disease (CHD) has decreased,¹ at least in part due to evidence-based medical therapies. Multiple primary and secondary prevention trials have clearly established statin therapy as one of the most effective pharmacological interventions for lowering CVD risk. A recent systematic review

of all statin trials by the United States Preventive Services Task Force showed a significant 8% reduction in all-cause mortality and a nearly 30% reduction in myocardial infarction, stroke, and composite cardiovascular outcomes.² However, despite optimal statin therapy, which is itself a daunting task, there remains an enormous burden of residual risk. Additional lipid-lowering therapy may address some of this need. The 2 main reasons for considering nonstatin therapies include statin intolerance and continued elevation of atherogenic lipoproteins despite optimal statin therapy.

Clinical trials have reported a relatively low incidence of statin intolerance, yet in clinical practice, it is a significant problem. Some observational studies have reported a prevalence of 10% to 25%, contributing to a nearly 50% nonadherence rate.³ While many of these patients can be managed by changing the statin type, dose, or frequency, a substantial proportion cannot tolerate statins and require nonstatin therapy for risk reduction.

In addition to this group of patients, many others have elevated levels of atherogenic lipoproteins, including low-density lipoproteins (LDL), triglyceride-rich lipoproteins such as remnant particles, and lipoprotein (a), and require the addition of nonstatin therapies for further risk reduction. This is especially true in patients with severe hypercholesterolemia, such as those with heterozygous or homozygous familial hypercholesterolemia (FH). Nonstatin therapies have significantly changed the treatment landscape for these patients and will be the main focus of this chapter. Triglyceride- and lipoprotein (a)-lowering therapies have been the subject of other presentations and reviews and are not discussed here.

Practice Gaps

- Identifying patients who remain at high risk for CVD despite maximal tolerated statin therapy.
- Identifying optimal therapies for patients who remain at high risk for CVD despite maximal tolerated statin therapy. Multiple drug categories, in addition to statins, reduce LDL-cholesterol concentrations. However, they have not consistently been shown to reduce the risk of CVD. It is important to identify appropriate patient groups for whom adding nonstatin therapies would be beneficial.
- Understanding the cost and adverse-effect implications of nonstatin therapies. Because lipid-lowering therapy for CVD risk reduction is a lifelong intervention and many of the novel therapies are expensive, a thorough consideration of both safety and cost must be undertaken before recommending nonstatin therapies.

Discussion

Statins are the first-line pharmacological intervention for CVD risk reduction in most patients, but as discussed above, many patients require additional or alternative therapies. The 2 main categories of patients with hypercholesterolemia who require nonstatin therapies are those with statin intolerance and those with severe hypercholesterolemia or high CVD risk who need more aggressive lipid-lowering.

Statin Intolerance

Statin intolerance, primarily due to muscle adverse effects, is common in clinical practice. It is defined as 1 or more adverse effects associated with statin therapy that resolve or improve with a dosage reduction or discontinuation.^{4,5} Muscle symptoms (eg, myalgia, myopathy, or rhabdomyolysis) are the most common adverse effects leading to statin intolerance. Typically, patients are considered statin intolerant if they cannot tolerate

a minimum of 2 statins, including at least 1 at the lowest approved daily dosage. More recently, some experts have begun distinguishing between complete and partial intolerance, with the latter denoting the inability to tolerate the dosage required to achieve the patient-specific therapeutic objective. The prevalence of statin intolerance ranges from 5% to 30%, with higher rates reported in observational studies than in clinical trials. When managing the care of patients with statin intolerance, it is important to address any modifiable risk factors, such as hypothyroidism, severe vitamin D deficiency, and drug-drug interaction with concomitant CYP inhibitors (eg, cyclosporine, digoxin, and antimicrobial agents such as certain macrolides and ketoconazole). Other strategies, such as reducing the dose, switching to nondaily dosing, or switching statins (eg, from a lipophilic statin such as atorvastatin to a hydrophilic statin such as rosuvastatin), should be explored before concluding that the patient has statin intolerance. In patients at high risk who have statin intolerance, nonstatin therapies should be considered. In patients with a rare form of statin-induced immune necrotizing myopathy, only nonstatin therapies should be considered.

Familial Hypercholesterolemia

Another group of patients who require consideration of nonstatin therapies includes those with FH or those with nonmonogenic severe hypercholesterolemia. FH is one of the most common genetic disorders, with a reported prevalence of 1 in 250 for the heterozygous form. Homozygous FH is quite rare, with an estimated prevalence of 1 in 1 million, although some recent estimates are closer to 1 in 250,000. Autosomal dominant FH is due to pathogenic variants in the gene encoding the LDL receptor, defective apolipoprotein B, or activating pathogenic variants in the *PCSK9* gene. Typically, LDL-cholesterol concentrations range from 200 to 400 mg/dL (5.18-10.36 mmol/L) in patients with heterozygous FH, whereas they exceed 500 mg/dL (>12.95 mmol/L) in homozygous patients. They

are at extremely high risk for premature CVD and need aggressive lipid-lowering therapy initiated at a young age. Previously, a 50% reduction from the baseline LDL-cholesterol level was considered a satisfactory goal of lipid-lowering therapy, but with the advent of novel nonstatin therapies, it is reasonable to target more aggressive goals, such as less than 100 mg/dL (<2.59 mmol/L) for primary prevention and less than 70 mg/dL (<1.81 mmol/L) for secondary prevention.

Statins are the first drug of choice for CVD risk reduction in all patients, including those with FH. The mechanism of action of statins involves reducing endogenous cholesterol synthesis by inhibiting HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. This leads to upregulation of LDL-receptor expression and enhanced clearance of circulating LDL particles. Other drugs that lower LDL-cholesterol concentrations are briefly discussed in the following sections.

Ezetimibe

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption and indirectly increases hepatic LDL-receptor expression. It binds to the NPC1L1 receptor in the intestines and liver and may also influence net hepatic cholesterol excretion. Cholesterol reduction is typically more modest than with statins, ranging from 17% to 25%, depending on whether it is used as monotherapy or in combination with statin therapy. In addition to lowering LDL cholesterol, there is a concomitant reduction in apolipoprotein B. In the IMPROVE-IT trial,⁶ a large randomized controlled trial of more than 18,000 patients with postacute coronary syndrome, a combination of simvastatin and ezetimibe significantly reduced the composite endpoint compared with simvastatin alone. Subgroup analysis of this trial showed that the risk reduction with the addition of ezetimibe in patients with type 2 diabetes was nearly twice that in those without diabetes (13% vs 7%). Ezetimibe is relatively inexpensive and well-tolerated and should be the first option as add-on therapy to statins.

Bempedoic Acid

Bempedoic acid is a relatively novel cholesterol-lowering medication with a mechanism of action similar to that of statins. It reduces endogenous cholesterol synthesis, thereby increasing LDL-receptor expression and LDL particle clearance. Unlike statins, which inhibit HMG-CoA reductase, bempedoic acid inhibits ATP citrate lyase, which catalyzes a more proximal step in cholesterol biosynthesis. It is a prodrug that must be activated by a long-chain acyl CoA synthetase, which is present only in the liver and not in skeletal muscle. Therefore, its effects are largely limited to the liver, and it is less likely to cause muscle-related adverse effects, such as those seen with statin therapy, which may result from statin-induced reductions in cholesterol and other biological intermediates in skeletal muscle. Indeed, bempedoic acid has been extensively studied in statin-intolerant patients. In the CLEAR Serenity and CLEAR Tranquility studies, it reduced LDL cholesterol by about 25% and high-sensitivity C-reactive protein by about 30%.^{7,8} In the CLEAR Outcomes study⁹ involving nearly 14,000 statin-intolerant patients at high risk, bempedoic acid reduced the relative risk of a composite 4-point major adverse cardiovascular event by 13% and of fatal and nonfatal myocardial infarction by 23%. Subgroup analysis of about 4000 patients without established CVD in this trial showed a 30% reduction in relative risk.¹⁰ Bempedoic acid has been approved for LDL-cholesterol lowering and for primary and secondary prevention in individuals at high-risk. Although it is generally well tolerated, it may increase the risk of hyperuricemia and gout, which should be monitored in patients with previously elevated uric acid levels. It has not been associated with hyperglycemia or an increased risk of diabetes, and there is a tendency toward a lower incidence of new-onset diabetes compared with placebo groups.

PCSK9 Inhibitors

PCSK9 is a serine protease that regulates LDL-receptor activity. When the LDL receptor is associated with PCSK9, it cannot dissociate from the endosome after internalization, leading to lysosomal degradation. Activating pathogenic variants in the *PCSK9* gene were first identified as a cause of monogenic autosomal dominant FH. Subsequently, patients with inactivating *PCSK9* variants were observed to have modest reductions in LDL cholesterol and a low risk of CVD, prompting the development of pharmacological agents that decrease PCSK9 activity. These include monoclonal antibodies to PCSK9 and a small interfering RNA (siRNA).

Evolocumab and alirocumab are the 2 commonly used monoclonal antibodies to PCSK9. They are usually administered as subcutaneous injections every 2 weeks and have been shown to produce an additional 50% to 60% reduction in LDL cholesterol when added to ongoing statin therapy. Significant reductions in clinical endpoints have also been demonstrated. The FOURIER trial¹¹ involving more than 27,000 patients with established CVD showed a 15% relative risk reduction when evolocumab was added to ongoing maximally tolerated lipid-lowering therapy. The mean LDL-cholesterol concentration was 30 mg/dL (0.78 mmol/L) in the evolocumab group compared with 92 mg/dL (2.38 mmol/L) in the control group, and there was no difference in the incidence of any adverse effects. Similar results have been observed in the alirocumab outcome trials.¹²

Inclisiran is a double-stranded siRNA taken up by hepatocytes, where it activates an RNA-induced silencing complex that targets PCSK9 mRNA, leading to prolonged lowering of PCSK9 levels in hepatocytes and a subsequent increase in LDL-receptor activity. A single 300 mg dose maintains a nearly 50% reduction in LDL-cholesterol for up to 6 months.¹³ In the ORION-9 trial,¹⁴ which enrolled 482 patients with heterozygous FH, inclisiran therapy achieved LDL-cholesterol concentrations below 100 mg/dL (<2.59 mmol/L) in 65% of patients and below 70 mg/dL (<1.81 mmol/L)

in 40% of patients. While outcome data are not yet available, inclisiran is approved for patients with heterozygous FH or those with established CVD who have elevated LDL-cholesterol concentrations on maximally tolerated statin therapy. In addition, it has recently been approved for primary prevention in other patients with hypercholesterolemia and high CVD risk. It is available as a single-dose prefilled syringe (284 mg/1.5 mL) and is administered subcutaneously by a health care provider. The initial injection is followed by a second injection in 3 months, then every 6 months. Although there are no head-to-head trials comparing the efficacy of inclisiran with that of PCSK9 monoclonal antibodies, the magnitude of LDL-cholesterol lowering is similar, with the potential for greater long-term adherence.

Evinacumab

Evinacumab is a monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3), an inhibitor of plasma lipases. The exact mechanism by which it lowers LDL cholesterol, especially in patients without functional LDL receptors, is unclear but may involve decreased LDL-particle synthesis through its action on endothelial lipase. A nearly 50% reduction in LDL cholesterol has been observed in patients with severe refractory hypercholesterolemia and in those with homozygous FH who were on maximally tolerated statin therapy and PCSK9 inhibitors.¹⁵ Based on these studies, the US FDA approved evinacumab for the treatment of homozygous FH as an adjunct to other lipid-lowering therapies in individuals older than 12 years. It is administered either intravenously (15 mg/kg every 4 weeks) or subcutaneously (300-450 mg every 1 to 2 weeks). Clinical outcome data are unavailable, and it is quite expensive (approximately \$450,000/year). It is not currently approved for use in any patient population other than those with homozygous FH.

Clinical Case Vignettes

Case 1

A 56-year-old man is evaluated to optimize lipid-lowering therapy after stopping atorvastatin, 10 mg daily, because of thigh pain and weakness. He was initially taking 20 mg daily, and decreasing the dose did not improve his symptoms. He had previously been on rosuvastatin, 10 mg daily, and had experienced similar symptoms after a few weeks. Even with rosuvastatin, 5 mg twice weekly, he found it difficult to exercise and eventually stopped taking it. He does not have established CVD but is concerned because his father had a myocardial infarction at age 62 years. He has prediabetes and mild hypertension that is well controlled on low-dosage amlodipine. He does not use tobacco products and tries to exercise most days of the week. He eats a mostly plant-based diet and consumes alcohol only occasionally.

Lipid panel (on no medications):

Total cholesterol = 236 mg/dL (SI: 6.11 mmol/L)
 Triglycerides = 210 mg/dL (SI: 2.37 mmol/L)
 HDL cholesterol = 43 mg/dL (SI: 1.11 mmol/L)
 LDL cholesterol = 148 mg/dL (SI: 3.83 mmol/L)
 Apolipoprotein B = 136 mg/dL (SI: 1.36 g/L)
 High-sensitivity C-reactive protein = 3.6 mg/L
 (SI: 34.3 nmol/L)

Which of the following is the best recommendation for lipid-lowering and CVD risk reduction?

- A. Pravastatin 20 mg
- B. Retrial of atorvastatin, 10 mg, with CoQ-10 supplement
- C. Ezetimibe, 10 mg daily
- D. Bempedoic acid, 180 mg daily
- E. Stanol ester supplement

Answer: D) Bempedoic acid, 180 mg daily

This patient has multiple risk factors, including a family history of premature CVD, prediabetes, hypertension, and atherogenic dyslipidemia. He would benefit from aggressive risk factor modification, including lipid-lowering therapy.

Unfortunately, he has tried 2 statins and could not tolerate them, even at very low dosages. These included a lipid-soluble statin (atorvastatin) and a water-soluble statin (rosuvastatin), making it rather unlikely that he will tolerate another statin, such as pravastatin (Answer A). This would have been a good choice if he were taking multiple other medications and drug-drug interactions had contributed to the statin adverse effects. Despite initial promise and a few anecdotal reports, CoQ10 supplementation (Answer B) has not been shown to be effective for statin-associated muscle adverse effects in well-controlled trials. Although stanol ester supplements (Answer E) may modestly lower LDL cholesterol, there are no data supporting a reduction in CVD risk. It would be more reasonable to use them as adjuncts to other lipid-lowering therapies. Of the remaining options, both ezetimibe (Answer C) and bempedoic acid (Answer D) are reasonable choices. Bempedoic acid is preferable, as it is indicated for both lipid-lowering and primary prevention based on clinical trials. Because this patient also has elevated high-sensitivity C-reactive protein, bempedoic acid is a better choice, as it reduces it more than ezetimibe. Based on the response to bempedoic acid, we can consider adding ezetimibe as a next step.

Case 2

A 64-year-old man with a 6-year history of type 2 diabetes presents for recommendations on lipid-lowering therapy. He is currently taking atorvastatin, 80 mg daily, and is tolerating it well. Diabetes is well controlled on metformin, 1000 mg twice daily, and semaglutide, 2 mg once weekly, with a hemoglobin A_{1c} level of 6.9% (52 mmol/mol). He has no known chronic complications of diabetes. Hypertension is well controlled on lisinopril, 20 mg daily. He has gained 2 lb (0.9 kg) since the last visit (BMI = 32.3 kg/m²) because he has been less active due to gout flares. He is confident he will lose the excess weight after resuming allopurinol and regular walking.

Lipid panel:

Total cholesterol = 186 mg/dL (SI: 4.82 mmol/L)
 Triglycerides = 215 mg/dL (SI: 2.43 mmol/L)
 HDL cholesterol = 44 mg/dL (SI: 1.14 mmol/L)
 LDL cholesterol = 87 mg/dL (SI: 2.25 mmol/L)

In addition to advice on intensifying weight-loss efforts, which of the following is the best next step?

- A. Continue atorvastatin, repeat lipid panel in 3 months
- B. Add ezetimibe, 10 mg daily
- C. Add bempedoic acid, 180 mg daily
- D. Add colesevelam, 6 tablets of 625 mg daily
- E. Add evolocumab, 140 mg every 2 weeks

Answer: B) Add ezetimibe, 10 mg daily

This patient is at high risk of CVD given longstanding type 2 diabetes. He also has metabolic syndrome with obesity and atherogenic dyslipidemia. Although he does not have established CVD, it is reasonable to treat him aggressively with intensified lipid-lowering therapy, aiming for an LDL-cholesterol threshold of at least 70 mg/dL (1.81 mmol/L) (or, more appropriately, a non-HDL-cholesterol threshold of 100 mg/dL [2.59 mmol/L]). Simply continuing atorvastatin (Answer A) is not adequate. The safest and least expensive option that would provide more robust lipid lowering is the addition of ezetimibe (Answer B). In the IMPROVE-IT trial, patients with diabetes had twice the risk reduction compared with other participants. Bempedoic acid (Answer C) is also likely to be beneficial, but it can trigger gout flares by increasing uric acid levels. Colesevelam (Answer D) is a bile acid-binding resin that can lower LDL cholesterol but may worsen hypertriglyceridemia. Moreover, it has not been demonstrated to lower CVD risk when used with statin therapy. Evolocumab (Answer E) would certainly be expected to significantly lower LDL and non-HDL cholesterol and reduce risk, but it is substantially more expensive than generic ezetimibe. It is currently approved only

for secondary prevention or for the treatment of patients with heterozygous FH.

Case 3

A 32-year-old man with severe hypercholesterolemia is seen for evaluation. There is a strong family history of hypercholesterolemia, including both parents and multiple uncles. His father underwent angioplasty with stent placement at age 48 years. At age 18, the patient's LDL-cholesterol concentration was 480 mg/dL (12.43 mmol/L), and atorvastatin was initiated. Over the years, other therapies were added, and his current medications include atorvastatin, 80 mg daily; ezetimibe, 10 mg daily; and evolocumab, 140 mg every 2 weeks. He feels well and has no symptoms of CVD. He does not smoke cigarettes and has a healthy intake of fruits and vegetables. Thickening of the Achilles tendons is noted.

Fasting lipid panel:

Total cholesterol = 230 mg/dL (SI: 5.96 mmol/L)
 Triglycerides = 110 mg/dL (SI: 1.24 mmol/L)
 HDL cholesterol = 55 mg/dL (SI: 1.42 mmol/L)
 LDL cholesterol = 156 mg/dL (SI: 4.04 mmol/L)

Which of the following is the best next step in this patient's management?

- A. Continue current medications and recommend no changes
- B. Change atorvastatin, 80 mg, to rosuvastatin, 40 mg, and continue other medications
- C. Add inclisiran
- D. Add evinacumab
- E. Start biweekly LDL apheresis

Answer: D) Add evinacumab

This patient likely has homozygous FH. Both parents have hypercholesterolemia, and his father has premature CVD. As a teenager, his LDL-cholesterol concentration was close to 500 mg/dL (12.95 mmol/L) before treatment, and he developed tendon xanthomas at a young age. These features support the diagnosis of

homozygous FH, which was confirmed by genetic testing revealing biallelic pathogenic variants in the LDL-receptor gene. He has been on an appropriately aggressive combination lipid-lowering therapy with a fairly good response. Compared with his baseline, his LDL cholesterol has decreased by more than 60%. However, the achieved LDL-cholesterol concentration remains quite high at 156 mg/dL (4.04 mmol/L), and further lowering it would be even more beneficial for reducing his risk of CVD. Therefore, making no changes (Answer A) is inappropriate, and switching one high-intensity statin for another (Answer B) is unlikely to make a significant difference. He is already on a PCSK9 monoclonal antibody, evolocumab, and adding another PCSK9 agent, such as inclisiran (Answer C), an siRNA against PCSK9, is unlikely to have much effect on his lipid profile. However, the ANGPTL3 monoclonal antibody evinacumab (Answer D) has been shown to further reduce LDL cholesterol by more than 40% in patients with homozygous FH and severe hypercholesterolemia. It is an approved therapy for homozygous FH and may help avoid LDL apheresis (Answer E), which is cumbersome and inconvenient. Other approved medical therapies for homozygous FH include mipomersen, an antisense oligonucleotide to apolipoprotein B, and lomitapide, an oral small molecule that inhibits microsomal triglyceride transfer protein. Both therapies decrease

VLDL synthesis in the liver and, therefore, the subsequent generation of LDL particles. They are also very expensive and have the potential to cause hepatic steatosis.

Key Learning Points

- CVD is the leading cause of death worldwide, yet it has a long latent period, making it amenable to preventive therapies.
- Among pharmacological interventions, statins have demonstrated consistent efficacy in both primary and secondary prevention trials and are the cornerstone of lipid-lowering therapy for reducing CVD risk.
- Despite optimal statin therapy, there remains an enormous burden of residual risk. Furthermore, many patients cannot tolerate statin therapy at adequate intensity.
- Nonstatin drugs that reduce total and LDL-cholesterol levels include ezetimibe, bempedoic acid, PCSK9 inhibitors (monoclonal antibodies and siRNA), and evinacumab.
- Ezetimibe and PCSK9 monoclonal antibodies reduce CVD risk when added to ongoing statin therapy. Bempedoic acid reduces the risk of adverse effects in statin-intolerant individuals. Evinacumab is approved for patients with homozygous FH.

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Evaluation and Management of Primary Aldosteronism

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Diagnose primary aldosteronism.
- Initiate treatment for primary aldosteronism.

Significance of the Clinical Problem

Primary aldosteronism is an endocrinopathy characterized by dysregulated aldosterone production that occurs despite relative suppression of renin and angiotensin II and is relatively unsuppressible by volume and sodium-loading maneuvers. Most underlying causes of primary aldosteronism involve pathogenic somatic variants in the adrenal cortex that drive constitutive aldosterone production, superimposed on dysregulated aldosterone stimulation by aberrant hormonal and nonhormonal receptors and ligands, such as ACTH, angiotensin II, LH/hCG, GIP, vasopressin, and others.^{1,2} Primary aldosteronism increases the risk for adverse cardiometabolic and kidney outcomes. The public health relevance of this is underscored by the fact that overt primary aldosteronism can be detected in at least 10% to 20% of people with hypertension; however, a substantially higher proportion of people with hypertension have milder renin-independent aldosterone production that represents a pathologic continuum of primary aldosteronism pathophysiology that also imparts cardiorenal risk.³⁻⁵

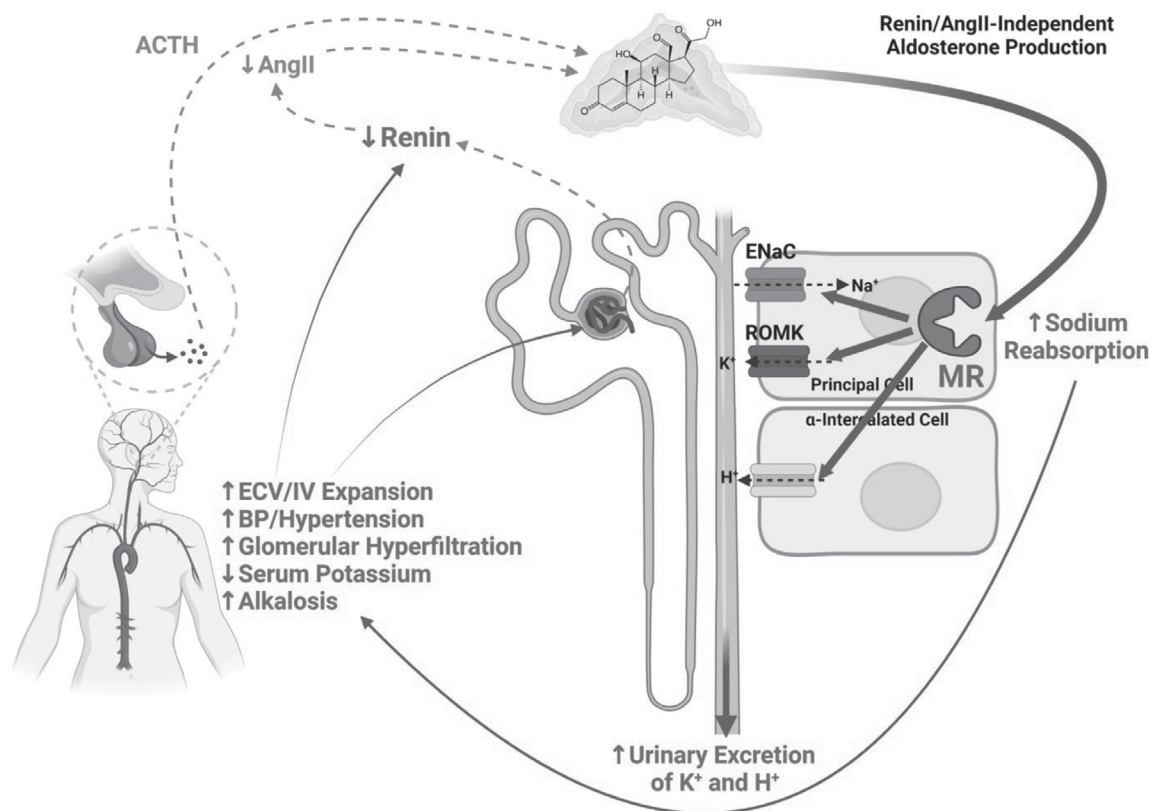
Primary aldosteronism pathophysiology increases activation of the mineralocorticoid receptor (MR) in the kidneys, leading to volume expansion and hypertension, and in extrarenal tissues, resulting in increased inflammation, fibrosis, and adverse cardiometabolic and kidney outcomes (*Figure 1, following page*).⁶ Importantly, the pathophysiology of primary aldosteronism contributes to adverse outcomes beyond those attributable to hypertension alone. For these reasons, it is imperative that patients with primary aldosteronism be treated with targeted therapy to abolish or neutralize the deleterious effects of aldosterone excess.

This chapter highlights 3 clinical vignettes that demonstrate approaches to diagnosing and treating primary aldosteronism.

Practice Gaps

- A minority of eligible patients are ever tested for primary aldosteronism, in part because previous guidelines endorse complex testing requirements, intimidating protocols, labor-intensive medication washouts, and heterogeneous diagnostic interpretations. Simplified guidance for testing and diagnosing primary aldosteronism would greatly improve diagnostic yields and the treatment of eligible patients.
- Most patients with primary aldosteronism are ultimately treated medically rather than surgically; therefore, guidance on optimizing medical therapy and on monitoring patients longitudinally is necessary.

Figure 1. Pathophysiology of Primary Aldosteronism



Aldosterone is physiologically regulated by the renin-angiotensin system, ACTH, and potassium. In primary aldosteronism, 1 or both adrenal glands contain foci of dysregulated aldosterone synthase expression that produce aldosterone independent of stimuli by angiotensin II and/or ACTH. This excess aldosterone production activates the MR in principal cells, even in volume-expanded states when renin and angiotensin II are suppressed, leading to inappropriate sodium reabsorption via ENaC and a commensurate excretion of potassium and hydrogen ions. This vicious cycle can induce the clinical manifestations of elevated blood pressure and hypertension, glomerular hyperfiltration, hypokalemia, and metabolic alkalosis. Abbreviations: Ang II, angiotensin II; BP, blood pressure; ECV, extracellular volume; ENaC, epithelial sodium channel; H⁺, hydrogen; IV, intravascular; K⁺, potassium; MR, mineralocorticoid receptor; Na⁺, sodium; ROMK, renal outer medullary potassium channel. Created with biorender.com. Reprinted from Hundemer GL et al. *Endocrine Reviews*, 2024; 45(1): 69–94. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

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Discussion

Given that fewer than 2% of patients at high risk are ever tested for primary aldosteronism, the updated 2025 Endocrine Society guidelines recommend several pragmatic steps to increase detection of this disorder (*Figure 2, following page*)⁷. A summary of these major updates includes:

1. **A suggestion to test all patients with hypertension.** Testing every patient with hypertension increases the likelihood that primary aldosteronism will be diagnosed before major adverse cardiovascular outcomes occur.
2. **Testing can be performed without obligate changes to antihypertensive medications.** Not requiring medication changes before testing removes a major barrier and should prompt more clinicians to proceed with testing. Most antihypertensive medications can lead to a false-negative result by raising renin and/or lowering aldosterone; therefore, a positive result despite their use is the simplest way to establish a diagnosis. When test results are unclear or false-negative or false-positive results are suspected, selective medication washout can be performed.
3. **Liberalized interpretations of test results.** Lowering the thresholds for what constitutes

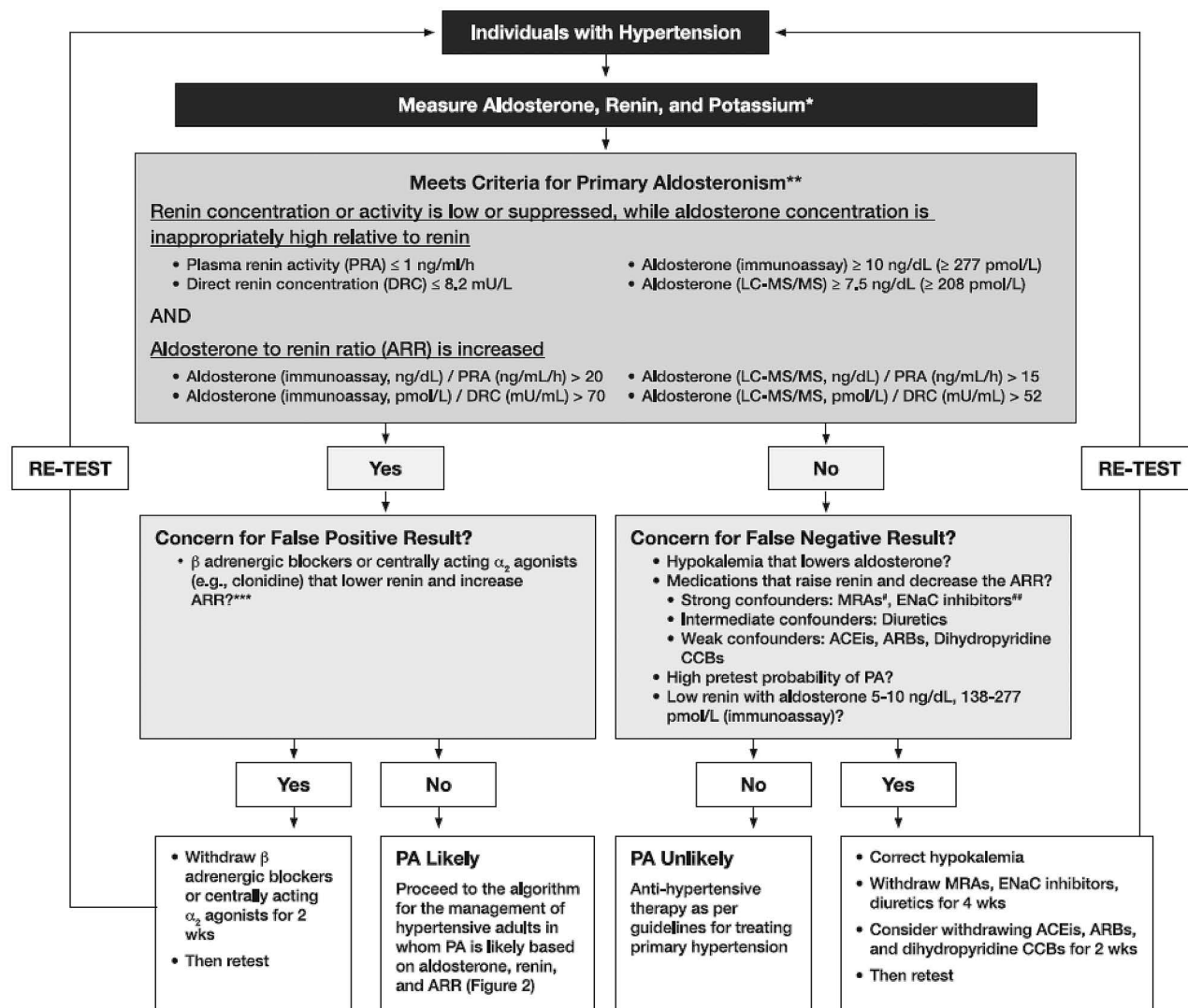
inappropriate renin-independent aldosterone production ensures that mild-to-moderate cases of primary aldosteronism will not be erroneously excluded.

4. **When results are not diagnostic, the opportunity to retest is available.**
Evaluating the causes of false-negative results,

and less commonly false-positive results, provides clinicians with opportunities to refine the diagnostic probability in uncertain cases.

5. **Establishing the diagnosis of primary aldosteronism based solely on a renin value, an aldosterone value, and the aldosterone-to-renin ratio.** Removing the

Figure 2. Screening for Primary Aldosteronism in Individuals With Hypertension



This figure outlines the screening process for primary aldosteronism (PA) in individuals with hypertension. *Blood is obtained in the seated position in the morning; ideally without venous stasis (release the tourniquet after venipuncture and wait at least 5 seconds before withdrawing blood) to avoid artifactual potassium increases. **The aldosterone, renin, and aldosterone-to-renin ratio (ARR) values provided in this figure are for guidance. However, as with many diagnostic tests based on continuous variables, sensitivity and specificity depend on the selected threshold. Aldosterone and renin levels are further influenced by individual variability, local laboratory assays, and other factors. Where possible, clinicians should rely on local laboratory cut points, as assays may vary. No cut point is perfect—each carries a trade-off between false-positive and false-negative results. Therefore, results should be interpreted in the context of the patient's pretest probability of primary aldosteronism, along with any interfering medications and conditions. ***Consider potential false-positive results induced by β -adrenergic blockers when aldosterone is <15 ng/dL (<415 pmol/L) by immunoassay and <10 ng/dL (<277 pmol/L) by liquid chromatography–tandem mass spectrometry. #Drosiprenone in oral contraceptive pills is a mineralocorticoid receptor antagonist (MRA). ##Amiloride and triamterene are epithelial sodium channel (ENaC) inhibitors. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

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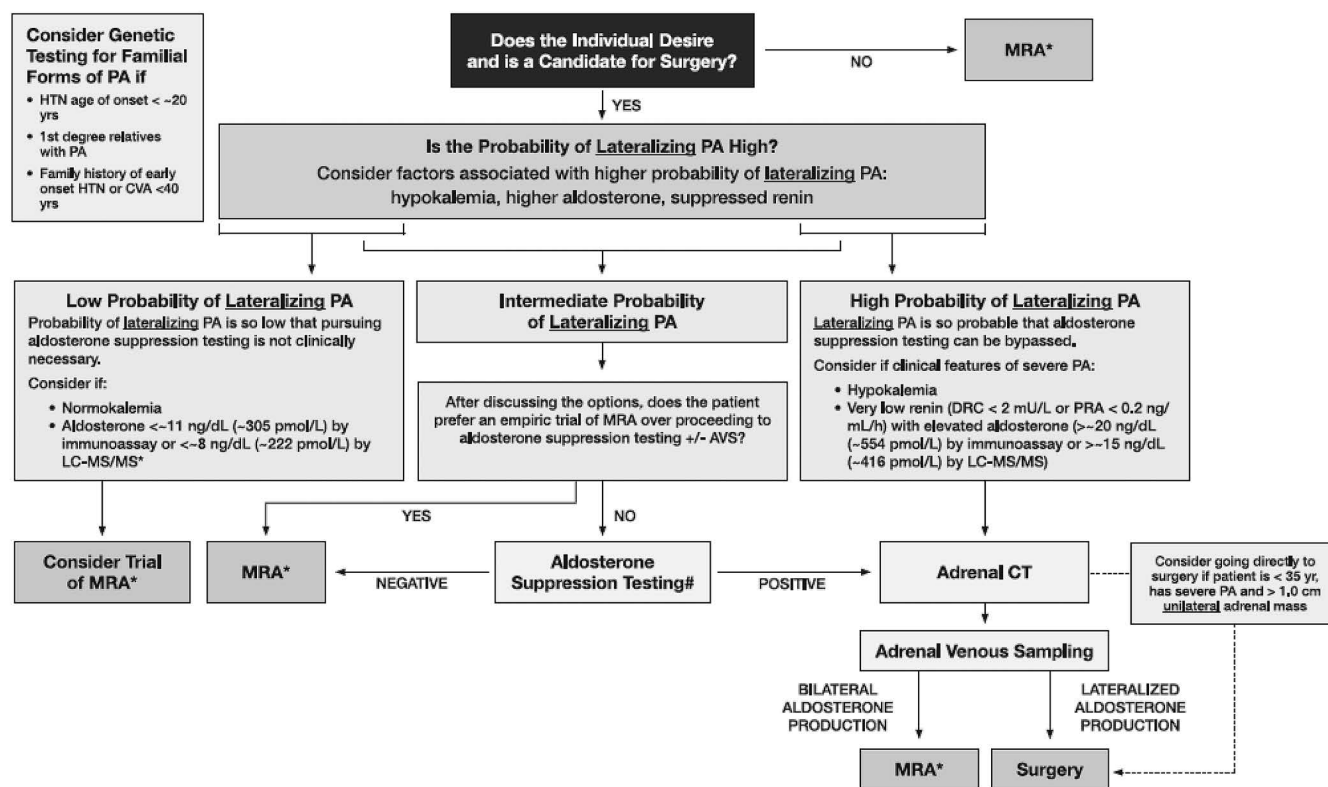
requirement for aldosterone-suppression testing (or confirmatory testing) simplifies the diagnostic pathway and eliminates critical barriers that are inaccurate and onerous.

Once a patient has a positive primary aldosteronism test, the diagnosis is assumed. In previous guidelines, more complex testing was usually required; however, the updated 2025 guidelines clarify that a positive primary aldosteronism test is sufficient for diagnosis. Clinicians should therefore focus on how best to treat the disorder, taking into account patient preferences, financial and resource considerations, geographical and social contexts,

and individual comfort levels. Importantly, algorithmic approaches always come second to personalized discussions between clinicians and their patients (*Figure 3*).⁷ A summary of these major updates includes:

1. **For patients who are not keen on surgical adrenalectomy or when adrenal venous sampling is unavailable, mineralocorticoid receptor antagonist (MRA) therapy should be initiated.** Moving directly to targeted therapy after a positive primary aldosteronism test streamlines the number of patients who are appropriately

Figure 3. Algorithm for the Management of Adults With Hypertension in Whom Primary Aldosteronism Is Likely



Patients likely to have primary aldosteronism (PA) who do not desire adrenalectomy or have contraindications to surgery can be offered mineralocorticoid receptor antagonist (MRA) therapy without further testing. MRA therapy is highly effective in PA. In addition, in studies of hypertensive individuals, MRAs consistently lower blood pressure more than alternative medication classes when renin is low or the aldosterone-to-renin ratio (ARR) is high. For patients interested in and capable of undergoing unilateral adrenalectomy, probabilistic and shared decision-making should be pursued. When the probability of lateralizing primary aldosteronism is low, patients can be offered MRA therapy without further testing. When the probability of lateralizing primary aldosteronism is high, cross-sectional adrenal imaging with CT and adrenal venous sampling can be performed to assess lateralization. When the probability of lateralizing primary aldosteronism is intermediate or uncertain, shared decision-making is advised. When possible, aldosterone-suppression testing may be considered to guide management in individuals willing and able to undergo testing. When interpreting the aldosterone-suppression test, one should consider the possibility of false-negative results. When aldosterone-suppression testing is not available or desired, MRA therapy can be initiated. Approximate values for aldosterone and renin are provided for guidance. *See Figure 5. Initiating and Monitoring MRA Therapy. #False negatives may occur, may be affected by local study conditions, and should be considered when deciding whether to proceed with adrenal venous sampling. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

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treated and underscores that most patients with primary aldosteronism are treated medically; thus, few obstacles should stand in the way of initiating medical treatment.

2. **For patients seeking to determine eligibility for adrenalectomy, and when adrenal venous sampling is available, probability-based decision-making is recommended.** Patients with milder primary aldosteronism typically have a higher probability of nonlateralizing disease, whereas those with severe primary aldosteronism typically have a higher probability of lateralizing disease. Although these probability-based assumptions are imperfect, they may be useful for clinicians and patients in settings with limited access to adrenal venous sampling and/or financial barriers. For patients with neither high nor low probability of lateralizing disease, severity (eg, the degree of renin-independent aldosteronism, the presence and severity of hypokalemia, and/or the presence of an adrenal tumor) and younger age may prompt adrenal venous sampling, as younger patients have greater lifelong exposure to the deleterious effects of aldosterone and therefore may have more person-years of benefit from adrenalectomy. Performing an aldosterone-suppression test in these instances has been suggested to quantify disease severity and triage decision-making, although multiple aldosterone-suppression tests exist, and their discriminatory capacity for predicting lateralizing disease is imperfect.
3. **Adrenal imaging is reserved for patients who are interested in surgery and undergoing adrenal venous sampling.** This recommendation simplifies previous guidelines, which called for universal imaging. The role of imaging is to provide an anatomic map for interventional radiologists and surgeons and to evaluate for an adrenal adenoma that may require testing for hypercortisolism. The incidence of aldosterone-producing adrenocortical

carcinoma is less than 1 in 1 million and, therefore, should not prompt routine imaging.

The main treatment modalities for primary aldosteronism include surgical adrenalectomy and MRA therapy. Other nonsurgical therapies that can be effective include dietary sodium restriction and epithelial sodium channel (ENaC) inhibitors. There is growing evidence that radiofrequency ablation and adrenal artery ablation can be effective in selected cases of lateralizing primary aldosteronism. Emerging evidence suggests that aldosterone synthase inhibitors may soon be an effective treatment option.

The effectiveness of surgical adrenalectomy in patients with lateralizing primary aldosteronism is characterized by attenuation of excess aldosterone production, thereby reducing blood pressure, normalizing serum potassium, and increasing renin. These biomarkers collectively indicate a reversal of the pathophysiology of primary aldosteronism and a restoration of normal physiology. When surgical adrenalectomy is pursued in patients with lateralizing primary aldosteronism, it can abolish or substantially reduce aldosteronism and correct hypokalemia, while improving blood pressure control. Surgical adrenalectomy can also be pursued in patients with nonlateralizing primary aldosteronism who have asymmetric disease or severe disease that is not amenable to medical therapy. In these cases, the objective of surgical adrenalectomy is to attenuate the severity of primary aldosteronism so that subsequent medical therapy is more likely to be successful (*Table, following page*).⁶⁻⁹

Most patients with primary aldosteronism are ultimately treated medically rather than surgically, owing to the fact that most cases are nonlateralizing, adrenal venous sampling is not available everywhere, and some patients prefer medical therapy. Medical therapy can be highly effective if titrated and monitored appropriately.⁶ Medical treatment options include dietary sodium restriction to decrease the substrate that fuels primary aldosteronism, MRAs to block the effects of aldosterone, ENaC inhibitors to block the effects of MR activation, and, potentially in the

future, aldosterone synthase inhibitors to decrease aldosterone production. The objectives of medical therapy for primary aldosteronism should be to restore normal physiology and attenuate excess cardiometabolic and kidney disease risk (Table). Ideally, dietary sodium restriction should be combined with MRA therapy to afford the greatest synergy. In cases of MRA intolerance, ENaC inhibitors can also be used to effectively improve blood pressure and hypokalemia⁷; however, this medication class does not block the extrarenal MR and therefore may not address deleterious aldosterone-MR interactions that contribute to cardiovascular injury.

Accruing evidence indicates that key biomarkers reflecting optimized medical therapy mirror the physiologic expectations after surgical adrenalectomy: blood pressure control with the fewest antihypertensive agents, normalization of serum potassium without supplementation, and a rise in renin. Adequate up-titration of MRA dosing should reverse volume expansion, which, in turn, should be reflected by a rise in renin (Figure 4, following page)⁶ Multiple studies have now shown that a rise in renin, from a suppressed to an unsuppressed state, is associated with

improved cardiovascular and kidney outcomes. This approach requires active titration of MRAs, usually at intervals of every few months, as shown in Figure 5 (following pages). In some patients, it may not be possible to raise renin due to the effects of high-dosage β -adrenergic blockers and/or chronic kidney disease; in these instances, renin may not be a useful biomarker, but blood pressure and potassium levels can still serve as proxies for optimized therapy. In patients with chronic kidney disease, increasing MRA dosing can increase the risk for hyperkalemia. In these instances, diuretics, SGLT-2 inhibitors, and novel potassium binders can be used to mitigate the risk of hyperkalemia and permit continued use of MRAs.

Clinical Case Vignettes

Case 1

A 70-year-old man with a history of hypertension and hypokalemia is taking 5 antihypertensive medications, yet his blood pressure remains elevated at 150-160/90-100 mm Hg. Testing for primary aldosteronism, performed without altering his medications, shows a plasma aldosterone concentration of 35 ng/dL (970 pmol/L),

Table. Expected Biochemical and Clinical Sequelae of Treatments for Primary Aldosteronism

Parameters	Adrenalectomy for Lateralizing Disease	Unilateral Adrenalectomy for Non-Lateralizing Disease	MR Antagonist Therapy	ENaC Inhibitors	Dietary Sodium Restriction
Aldosterone	↓↓	↓	↑	↑	↑
Renin	↑↑	↑↑	↑↑	↑↑	↑
ARR	↓↓	↓	↔/↓	↔/↓	↓
Serum Potassium	↑	↑	↑	↑	↑
Base Excess/ Alkalosis	↓	↓	↓	↓	↓
eGFR	↓	↓	↓	↓	↓
Blood Pressure	↓↓	↓	↓	↓	↓
Risk for Incident Cardiovascular and Kidney Disease	↓ [*]	unknown	↓ [*]	unknown	↓ [#]

Treatments for primary aldosteronism include curative adrenalectomy for lateralizing primary aldosteronism and noncurative unilateral adrenalectomy for nonlateralizing primary aldosteronism, MRA therapy, ENaC inhibitor therapy, and dietary sodium restriction. Abbreviations: ARR, aldosterone-to-renin ratio; eGFR, estimated glomerular filtration rate; ENaC, epithelial sodium channel; MR, mineralocorticoid receptor. ^{*}Observations from longitudinal cohort studies comparing curative adrenalectomy with MRA therapy. [#]Observations from population-based studies evaluating dietary sodium restriction in essential hypertension. Reprinted from Hundemer GL et al. *Endocrine Reviews*, 2024; 45(1): 69–94. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

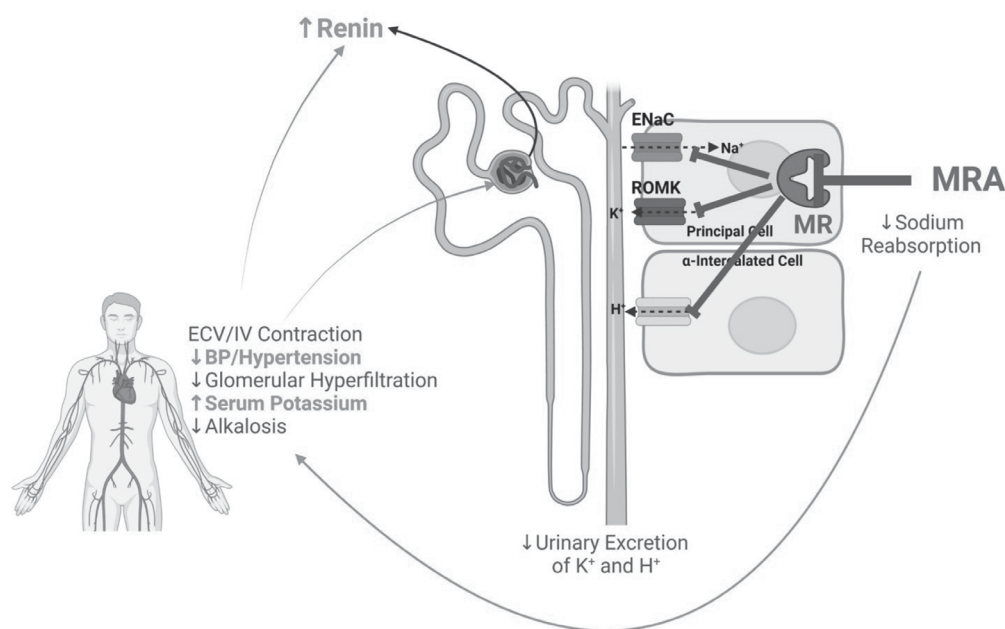
plasma renin activity of 0.50 ng/mL per h, and an aldosterone-to-renin ratio of 70 ng/dL per ng/mL/h (1940 pmol/L per ng/mL/h). He is diagnosed with primary aldosteronism. The patient expresses interest in assessing eligibility for adrenalectomy and is considered to have a reasonably high probability of lateralizing primary aldosteronism. He is referred for abdominal CT and adrenal venous sampling. Abdominal CT shows no discrete adrenal masses. Adrenal venous sampling demonstrates lateralization to the right side. He undergoes retroperitoneoscopic right adrenalectomy. Pathology reveals a subcentimeter adrenal adenoma without hyperplasia. Immunohistochemistry reveals that the adenoma is CYP11B2 positive (therefore, an aldosterone-producing adenoma). Additionally, multiple CYP11B2-positive aldosterone-producing micronodules are present in the adjacent adrenocortical tissue. Following the operation, he

requires 2 antihypertensive medications (down from 5) to maintain normal blood pressure. He is normokalemic, with renin of 4.4 ng/mL per h and aldosterone of 7.9 ng/dL (219 pmol/L).

How should this patient be counseled regarding future risk and follow-up?

- His primary aldosteronism is cured, but he will continue to have lifelong idiopathic hypertension
- His primary aldosteronism is in remission, but he should continue to be monitored longitudinally, as it may recur in the contralateral adrenal gland
- He has persistent primary aldosteronism and should now initiate MRA therapy
- He has persistent primary aldosteronism and should undergo a completion adrenalectomy

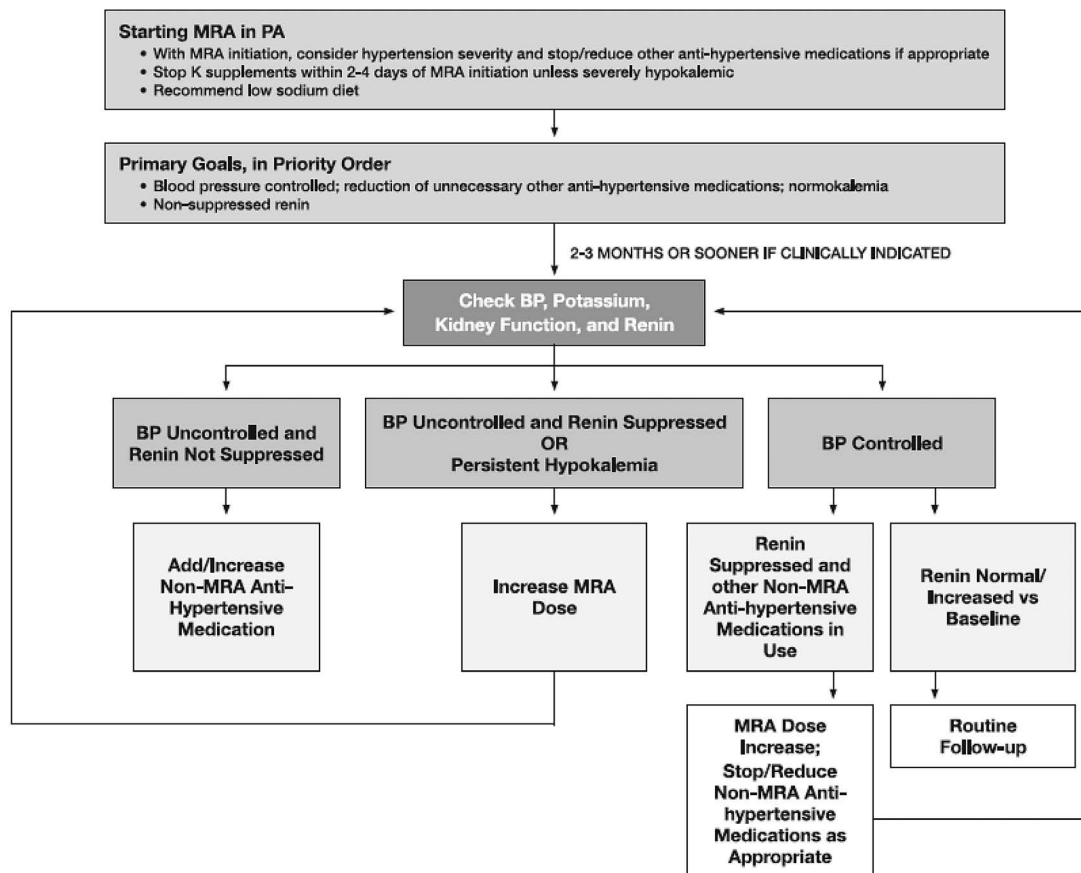
Figure 4. Biomarkers of Optimal Medical Therapy for Primary Aldosteronism



Through blockade of the interaction between aldosterone and the MR in the principal cell of the distal nephron, MRAs decrease ENaC-mediated sodium reabsorption. This, in turn, decreases volume expansion and urinary excretion of potassium and hydrogen ions. If the degree of MR blockade is sufficient to cause intravascular volume contraction and relative kidney hypoperfusion, renin secretion from the juxtaglomerular cells will rise. Thus, a rise in renin, along with a lowering of blood pressure and normalization of serum potassium, serves as a biomarker of adequate MR blockade in primary aldosteronism. In bold are the key biomarkers that reflect optimized medical therapy in primary aldosteronism: normalization of blood pressure and serum potassium, and a rise in renin. Abbreviations: BP, blood pressure; ECV, extracellular volume; ENaC, epithelial sodium channel; H⁺, hydrogen; IV, intravascular; K⁺, potassium; Na⁺, sodium; ROMK, renal outer medullary potassium channel. Created with biorender.com. Reprinted from Hundemer GL et al. *Endocrine Reviews*, 2024; 45(1): 69–94. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

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Figure 5. Initiating and Monitoring MRA Therapy



This is a general guide, and interpatient responsiveness to MRA dosing varies widely. MRA initiation and titration are often multistep processes. Each MRA adjustment is followed by assessment of blood pressure (BP) and biochemical response, then reentry into the treatment algorithm as appropriate. The primary therapeutic goal is BP control. The secondary goal is normokalemia. Measuring renin (as a marker of MR blockade) may assist in the process of MRA dose titration for achieving these goals and possibly reduce other non-MRA antihypertensive drugs. (1) Clinicians may start MRA at a relatively low dosage (spironolactone, 12.5-25 mg daily, or eplerenone, 25 mg daily or twice daily). Medically complex or frail individuals, and those at risk for MRA-drug interactions (eg, with an ACE inhibitor or ARB), may need careful monitoring. For individuals with more severe primary aldosteronism, especially with profound hypokalemia, a higher initial dosage could be considered (spironolactone, 50 mg daily, or eplerenone, 50 mg twice daily). (2) All individuals should have routine measurement of serum electrolytes, kidney function, and renin within 2 to 3 months of starting MRA therapy; more frequent serial measurements may be needed in those with prior severe hypokalemia or kidney impairment. Some panelists recommend inquiring about dietary sodium or measuring 24-hour urinary sodium at baseline and periodically during follow-up to track dietary salt restriction; a sodium target <85.5 mmol/d is recommended (representing <5 g/d salt intake). (3) MRA dosage changes to target BP control should occur at 8- to 12-week intervals, and the full drug effect may take up to 3 months in more severe forms of primary aldosteronism. Typical dosages required to de-suppress renin are variable and likely higher than dosages used empirically as add-on therapy for resistant hypertension; most individuals achieve renin de-suppression with spironolactone dosages (or spironolactone dosage equivalents) between 50 and 100 mg daily. Spironolactone may be increased in 25- to 50-mg increments, and eplerenone in 25- to 100-mg increments. With each MRA dosage change, repeat assessments of electrolytes, kidney function, and renin are recommended 2 to 3 months later. When possible, consider off-titration of other antihypertensive agents. Once renin is de-suppressed and further BP reduction is required, other non-MRA antihypertensive agents should be added or uptitrated. If BP is controlled on MRA monotherapy, there is insufficient evidence to support further increases in MRA dosage based solely on low renin levels. (4) Normalization of serum potassium usually occurs, even with lower-dosage MRAs, in the first 3 to 5 days, so it is reasonable to reduce or discontinue any potassium supplements 2 to 4 days after MRA initiation in all but the most severe hypokalemic cases. Individuals who require ongoing potassium supplementation require frequent, careful monitoring. Dietary salt restriction is a critical component of assessing the response to MRA therapy; individuals should be explicitly instructed in and assisted with dietary salt-reduction strategies. An ongoing high-salt diet is a very common reason for apparent nonresponse to MRA therapy. (5) Glomerular filtration rate (GFR) may decrease in individuals with primary aldosteronism on introduction of targeted medical therapy or with successive titration of MRA. The time course of change may be over days to weeks and, in most cases, represents a marker of treatment efficacy rather than an adverse effect. The natural history of an appropriate treatment-induced decrease in GFR is usually one of eventual long-term stability, suggesting a renal-sparing effect of effective MRA therapy. If kidney function progressively declines, consider referral to nephrology and discontinuation of ACE inhibitors or ARBs. (6) Gynecomastia from spironolactone is dose-related and may appear as early as 1 to 2 months into therapy, but more commonly after ≥6 months of treatment. In some cases (especially in younger males), reducing the dosage to ≤50 mg daily resolves gynecomastia. Some men may request a switch to a more selective MRA, such as eplerenone or other new MRA agents; amiloride is an alternative option. This almost always allows complete resolution of gynecomastia if it has not yet progressed to a large size. (7) Routine follow-up after MRA dose optimization should generally consist of blood pressure monitoring and annual measures of potassium and kidney function. Patients with chronic kidney disease or other risk factors for impaired kidney function/electrolyte disorders (eg, combination MRA and ACE inhibitor/ARB drugs) should undergo biochemical monitoring more frequently. Routine repeat renin measures are not necessary unless re-entering the MRA titration algorithm due to incomplete BP/potassium control. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

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Answer: B) His primary aldosteronism is in remission, but he should continue to be monitored longitudinally, as it may recur in the contralateral adrenal gland

This patient had resistant hypertension and hypokalemia, a clear diagnosis of primary aldosteronism, and a reasonably high suspicion for lateralizing disease. Testing was performed without holding medications and showed a low renin value and overt renin-independent aldosterone production, despite taking medications that may have raised renin (thiazide, ACE inhibitor) and lowered aldosterone (ACE inhibitor), potentially inducing a false-negative result. Thus, testing while on medications simplifies the approach and provides a “stress test” that increases confidence in the diagnosis. The patient was diagnosed with primary aldosteronism based on these values alone; there was no need to conduct dynamic aldosterone-suppression testing, given his established renin-independent aldosterone. The quality of evidence supporting the accuracy of this practice is low, particularly for confidently excluding the diagnosis. The absence of discrete adrenal adenomas on imaging is an important reminder that the presence of an adrenal mass does not imply that the mass is the source of primary aldosteronism, and the absence of an adrenal mass does not exclude the possibility of primary aldosteronism; most primary aldosteronism emanates from microscopic adrenal foci that harbor pathogenic somatic variants. This patient had lateralizing primary aldosteronism that was amenable to surgical adrenalectomy. The pathology provides important insights: although the disease was “unilateral,” it was caused by multiple foci of autonomous aldosterone production. This pathology is often referred to as multifocal or nonclassic, whereas the “classic” pathology refers to a single aldosterone-producing adenoma. Multifocal pathology implies that primary aldosteronism arises from multiple foci that develop asymmetrically and/or asynchronously in the adrenal cortex and may also affect the contralateral adrenal gland. Although this patient has no evidence of postoperative persistent primary aldosteronism

(renin is no longer low), a substantial proportion of patients with apparent remission of primary aldosteronism postoperatively can have recurrent disease in the future. For this reason, “cure” is likely a misnomer for many patients and should be replaced with “remission.” This patient has had an excellent outcome, which should correlate with substantial reductions in incident cardiorenal risk; however, he should be followed longitudinally (annually) and retested for primary aldosteronism periodically or if there is substantial worsening of his blood pressure and/or serum potassium.

Case 2

A 48-year-old man is diagnosed with primary aldosteronism. CT shows 3 right-sided adrenal adenomas (0.4–2.2 cm) and 1 subcentimeter left-sided adrenal adenoma. Adrenal venous sampling reveals a lateralization ratio of 2, favoring the right side and a lack of contralateral suppression. He is treated with eplerenone, amlodipine, and atenolol for nonlateralizing primary aldosteronism. Over the next few years, his eplerenone dosage is titrated to 500 mg daily. Despite this high dosage, his plasma renin activity remains suppressed (<0.6 ng/mL per h), he has persistent hypokalemia, his blood pressure is high, and he develops atrial fibrillation and a stroke. Given the severity of his disease, a unilateral right-sided laparoscopic adrenalectomy is performed. Postoperatively, he still has primary aldosteronism, but his blood pressure and potassium normalize with eplerenone, 50 mg daily, and amlodipine, and his renin rises to 1.4 ng/mL per h. However, 5 years later (at age 58 years), his blood pressure is again high and potassium is low despite eplerenone, 400 mg daily, amiloride, amlodipine, and losartan. In addition, his renin is undetectably low, and he develops heart failure with reduced ejection fraction (40%).

Which of the following is most likely to improve this patient's cardiovascular risk profile?

- A. Increase amiloride to 20 mg daily
- B. Increase eplerenone to 300 mg twice daily
- C. Substitute losartan for lisinopril, 40 mg daily
- D. Renal denervation
- E. Left-sided laparoscopic adrenalectomy

Answer: E) Left-sided laparoscopic adrenalectomy

In truth, there is no perfect correct answer to this scenario, as it represents a challenge that requires individualized management, discussion of risk tolerance, and multiple conversations between clinician and patient. The only choice likely to yield meaningful reductions in cardiovascular risk is completion adrenalectomy, which will essentially eliminate primary aldosteronism and induce primary adrenal insufficiency. All other options are unlikely to meaningfully reduce blood pressure but are likely to complicate pharmacotherapy and leave the patient at a high risk for progressive cardiovascular decline. This patient's remarkable response to unilateral (noncurative) adrenalectomy is a well-established phenomenon.^{8,9,14,15} Patients with nonlateralizing primary aldosteronism generally do very well with MRA treatment; however, a minority either cannot tolerate the medications or have progressive, severe disease that requires intensification of therapy. A unilateral, debulking adrenalectomy in nonlateralizing primary aldosteronism can substantially improve blood pressure control and potassium balance and raise renin levels. In some cases, primary aldosteronism may even go into remission. This patient experienced substantial improvements in disease severity with this procedure; although he had persistent primary aldosteronism, it was well-treated with low dosages of eplerenone and amlodipine. The most important biomarkers of MRA therapy are normalization of blood pressure and potassium. Beyond these factors, an increase in renin has been recognized as another predictor of outcomes.^{6,7,16-19} Renin is typically

low in primary aldosteronism, reflecting volume expansion due to MR overactivation (*Figure 4*). With gradual uptitration of MRAs (*Figure 5*), the pathophysiology of primary aldosteronism can be reversed or mitigated, and renin secretion increases.⁶ This rise in renin is associated with a lower risk of incident adverse cardiorenal outcomes, and guidelines now recommend an increase in renin as a treatment objective. This patient's disease gradually progressed, blood pressure rose, and renin declined, and he developed serious cardiovascular complications. Although primary adrenal insufficiency is not a condition that should be induced without serious consideration, this patient's quality of life, pharmacotherapy burden, and risk of adverse cardiovascular outcomes would all improve dramatically by trading primary adrenal insufficiency for primary aldosteronism. After nuanced discussions with an endocrinologist highly experienced in managing both primary aldosteronism and primary adrenal insufficiency, the patient underwent completion adrenalectomy, was educated on the importance of daily glucocorticoid and mineralocorticoid supplementation, and was taught about emergency sick-day steroid dosing.²⁰ Postoperatively, his blood pressure was normal with only amlodipine and hydrochlorothiazide, and he noted a substantial improvement in his quality of life and function over the subsequent 2 years.

Case 3

A 34-year-old-woman is evaluated for hypertension resistant to 3 antihypertensive agents. Her plasma aldosterone concentration is 21.7 ng/dL (602 pmol/L), direct renin concentration is 2 mU/L, and aldosterone-to-renin ratio is 11 ng/dL per mU/L (301 pmol/L per mU/L). She is diagnosed with primary aldosteronism and is interested in determining whether she is eligible for surgical adrenalectomy. Abdominal CT shows a 1.3-cm left adrenal adenoma, and dexamethasone-suppression testing excludes hypercortisolism. Adrenal

venous sampling performed with continuous ACTH infusion shows excellent selectivity indices indicating adequate sampling of adrenal venous blood, and reveals a lateralization index of 2.0, favoring the left side (lateralization index greater than 4.0 is typically considered the threshold for lateralization amenable to adrenalectomy).

How should this patient be counseled?

- A. She has nonlateralizing primary aldosteronism and should initiate lifelong MRA therapy
- B. Repeat adrenal venous sampling should be performed without ACTH infusion
- C. Left-sided adrenalectomy should be pursued
- D. B or C

Answer: D) B or C

This young woman has clear primary aldosteronism and resistant hypertension; strategies to mitigate her long-term cardiovascular risk are paramount. This objective could be achieved with either surgery or MRA therapy; however, given her young age, it would be preferable if she were a candidate for adrenalectomy, which could yield durable disease remission. There are many international protocols for adrenal venous sampling, but no single standardized method is widely accepted.^{21,22} Protocols include adrenal venous sampling with continuous ACTH infusion to maximize cortisol and aldosterone secretion, sampling without ACTH infusion to evaluate basal aldosterone secretion, and measuring adrenal venous hormones without and with ACTH infusion. The pros and cons of each approach are multifaceted. One advantage of ACTH infusion is that it substantially increases cortisol production, thereby facilitating easier confirmation of successful adrenal vein catheterization. In addition, ACTH can substantially increase aldosterone; however, some foci of autonomous aldosterone production do not express the ACTH receptor (MC2R) and thus may not respond as robustly. Thus, in some instances, ACTH infusion may stimulate physiologic aldosterone production more than

pathologic aldosterone production, reducing the lateralization index and potentially steering away from surgical adrenalectomy. In contrast, this issue is avoided when adrenal venous sampling is performed without ACTH; however, cortisol and aldosterone levels are lower without ACTH stimulation and may be borderline, raising doubts about the adequacy of adrenal vein catheterization. Of course, protocols that sample without and with ACTH have the advantages of both former protocols but require longer procedural time (including sedation time) and larger blood volume for sampling. For this patient, one option is to perform a left adrenalectomy, as there is some lateralization that will likely result in some or substantial postoperative disease improvement. This patient elected to repeat adrenal venous sampling without and with ACTH infusion; the lateralization index without ACTH was 14, favoring the left, confirming a dominant left-sided lateralizing source of primary aldosteronism. The patient underwent left laparoscopic adrenalectomy and postoperatively had normal blood pressure without the use of antihypertensive medications and had no biochemical evidence of residual primary aldosteronism.

Key Learning Points

- Primary aldosteronism is an endocrinopathy characterized by dysregulated aldosterone production that persists despite suppression of renin and angiotensin II, and that is not suppressed by volume and sodium-loading maneuvers. The underlying pathophysiology of primary aldosteronism increases the risk of adverse cardiometabolic and kidney outcomes.
- Diagnosis of primary aldosteronism can be simplified by testing nearly all patients with hypertension by measuring renin, aldosterone, and serum potassium, and by evaluating for renin-independent aldosterone production using the 2025 Endocrine Society guideline thresholds. Stopping antihypertensive medications is no longer required before

primary aldosteronism testing, and dynamic confirmatory testing is not required before initiating targeted medical therapy.

- For patients with lateralizing primary aldosteronism, surgical adrenalectomy is effective in attenuating excess aldosterone production, lowering blood pressure, normalizing serum potassium, and increasing renin—biomarkers that collectively indicate a reversal of pathophysiology and restoration of normal physiology.

- Most patients with primary aldosteronism are ultimately treated medically rather than surgically; the objectives of medical therapy in primary aldosteronism are to restore normal physiology and attenuate excess cardiometabolic and kidney disease risk.
- Accumulating evidence indicates that key biomarkers reflecting optimized medical therapy align with the physiologic expectations after surgical adrenalectomy: blood pressure control with the fewest antihypertensive agents, normalization of serum potassium without supplementation, and a rise in renin.

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DIABETES AND VASCULAR DISEASE

Updates in the Management of Diabetic Kidney Disease

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify and stage diabetic kidney disease (DKD) using contemporary criteria.
- Implement guideline-directed medical therapy (GDMT) to slow the progression of DKD.

Significance of the Clinical Problem

DKD remains one of the most consequential complications of diabetes and a leading cause of chronic kidney disease (CKD) and kidney failure worldwide.¹ Nearly 30% to 40% of individuals with diabetes develop evidence of kidney involvement, characterized by albuminuria and/or a progressive decline in estimated glomerular filtration rate (eGFR).^{2,3} DKD is the most common cause of end-stage kidney disease (ESKD) requiring dialysis or transplantation and is associated with markedly increased risks of cardiovascular events, heart failure, hospitalization, and premature mortality. Importantly, kidney disease in diabetes rarely occurs in isolation; it reflects a systemic cardio-kidney-metabolic syndrome in which vascular dysfunction, inflammation, and fibrosis drive multiorgan injury.^{1,3}

Despite major therapeutic advances—including renin-angiotensin system blockade, SGLT-2 inhibitors, GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor

antagonists—gaps in implementation still exist.³ Screening for albuminuria remains inconsistent, risk stratification is often delayed,^{3,4} and evidence-based therapies are underused or not titrated for maximum benefit.^{3,5} Consequently, many patients experience preventable progression to advanced CKD, dialysis, or cardiovascular death. The clinical challenge is no longer simply the lack of effective therapies, but also the need to systematically identify individuals at high risk earlier, integrate risk-based treatment intensification, and operationalize multidisciplinary care models that can meaningfully reduce the incidence of kidney failure and its devastating personal and societal consequences.

Practice Gaps

- Inadequate early detection and risk stratification of DKD.
- Underuse and suboptimal sequencing of evidence-based therapies for DKD.
- Limited integration of cardio-kidney-metabolic risk management.

Discussion

Approximately 1 in 3 individuals with diabetes develops evidence of kidney involvement, manifested by albuminuria and/or a progressive decline in eGFR.¹⁻³ Importantly, DKD is not solely a kidney disorder—it reflects systemic cardio-kidney-metabolic dysfunction characterized by endothelial injury, inflammation, oxidative stress,

and fibrosis.³ The presence of DKD substantially amplifies the risk of heart failure, atherosclerotic cardiovascular disease (ASCVD), hospitalization, and premature mortality.^{1,3} Indeed, many individuals with DKD are more likely to die from cardiovascular causes than to progress to needing dialysis, underscoring the urgency of integrated risk reduction.

Over the past decade, the therapeutic landscape has evolved dramatically. In addition to renin–angiotensin system (RAS) blockade,^{6,7} multiple large-scale trials have demonstrated that SGLT-2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), and nonsteroidal mineralocorticoid receptor antagonists (MRAs) significantly slow CKD progression, reduce heart failure hospitalizations, and lower cardiovascular mortality.^{8–12} These advances have shifted DKD management from reactive glycemic control toward proactive organ protection. However, despite the availability of effective therapies, substantial gaps in knowledge, skills, and practice persist, limiting their translation into improved patient outcomes.

Gap 1: Inadequate Early Detection and Risk Stratification of DKD

A foundational competency in DKD management is correctly identifying and staging kidney disease using both eGFR and the urinary albumin-to-creatinine ratio (UACR).^{3,5} Yet, albuminuria screening remains inconsistent in clinical practice, and abnormal results are frequently not confirmed with repeat testing. Many clinicians underappreciate the prognostic synergy between declining eGFR and persistent albuminuria or fail to recognize rapid eGFR slope decline as a marker of high risk.^{2,3} As a result, individuals at high risk may remain unidentified until advanced CKD develops, when therapeutic benefit is diminished. Improving physicians' competence in longitudinal risk assessment—rather than relying on single-laboratory thresholds—is critical to enabling timely intensification of therapy.

Gap 2: Therapeutic Inertia and Suboptimal Use of Evidence-Based Therapies

Although current guidelines strongly recommend SGLT-2 inhibitors for patients with diabetes and CKD,³ their real-world uptake remains suboptimal. Barriers include limited familiarity with trial evidence, concerns about transient eGFR reductions, uncertainty about therapy sequencing, and hesitation to manage adverse effects (eg, hyperkalemia with MRAs). Similarly, RAS blockade is often not titrated to maximally tolerated doses, and persistent albuminuria is not consistently treated as a modifiable therapeutic target.^{6,7}

This therapeutic inertia has measurable consequences. Failure to initiate or optimize kidney-protective therapies results in preventable CKD progression, higher rates of heart failure hospitalization, and increased mortality. Competency development must therefore extend beyond knowledge acquisition to include practical skills in medication initiation, dose titration, monitoring strategies, and patient counseling.

Gap 3: Fragmented Cardiovascular-Kidney-Metabolic Care

DKD exemplifies the interconnectedness of metabolic, kidney, and cardiovascular disease. However, care delivery often remains siloed among primary care, endocrinology, nephrology, and cardiology. Clinicians may focus narrowly on glycemic control while underemphasizing blood pressure optimization, lipid management, and heart failure risk mitigation. This fragmentation contributes to missed opportunities for comprehensive risk reduction.

Enhancing physician competence requires reframing DKD as a systemic vascular condition requiring coordinated, multidisciplinary management. Incorporating structured care pathways, shared decision-making models, and electronic health record–based clinical decision support can facilitate integrated, risk-based treatment strategies.

Conclusion

DKD represents a major and potentially modifiable driver of morbidity and mortality in individuals with diabetes. Although the therapeutic armamentarium has expanded significantly, gaps in physicians' knowledge, therapeutic inertia, fragmented care, and limited integration of longitudinal risk assessment continue to impede optimal implementation.

Addressing these competency gaps through education, systems redesign, and risk-based care pathways offers a high-yield opportunity to reduce kidney failure, cardiovascular events, and premature death. Strengthening physicians' expertise in DKD is therefore not only an educational priority but also a critical strategy for improving population-level outcomes in diabetes care.

Clinical Case Vignettes

Case

A 56-year-old woman with a 12-year history of type 2 diabetes presents for routine follow-up. Her comorbidities include hypertension and hyperlipidemia. Current medications include metformin, 1000 mg twice daily; amlodipine, 10 mg daily; and atorvastatin, 40 mg daily.

On physical examination, her blood pressure is 142/84 mm Hg, and BMI is 32 kg/m².

Laboratory results:

Hemoglobin A_{1c} = 7.4% (57 mmol/mol)
 eGFR = 60 mL/min per 1.73 m² (stable since last year)
 Urinary albumin-to-creatinine ratio (UACR) = 180 mg/g (previously not measured)
 Potassium = 4.4 mEq/L (SI: 4.4 mmol/L)

Which of the following is the most appropriate next step in management?

- A. Reassure the patient; kidney function is near normal
- B. Initiate an ACE inhibitor or ARB and repeat UACR to confirm persistent albuminuria

- C. Increase the metformin dosage to improve glycemic control
- D. Refer to nephrology immediately due to CKD
- E. Stop atorvastatin to reduce kidney burden

Answer: B) Initiate an ACE inhibitor or ARB and repeat UACR to confirm persistent albuminuria

This patient has stage 2 CKD (eGFR = 60 mL/min per 1.73 m²) with moderately increased albuminuria (A2 category). Albuminuria is a strong predictor of kidney progression and cardiovascular risk, even when eGFR is relatively preserved.

Best practice (Answer B) includes:

- Confirming persistent albuminuria (repeat testing ≥3 months)
- Initiating RAS blockade
- Optimizing blood pressure

Immediate nephrology referral (Answer D) is not mandatory at this stage unless there is a rapid decline, severe albuminuria, or diagnostic uncertainty. Reassurance (Answer A) reflects a common practice gap—under-recognition of albuminuria as clinically significant. Glycemic intensification alone (Answer C) does not provide an organ-protective benefit equivalent to that of RAS blockade. Statins (Answer E) remain indicated because of her elevated ASCVD risk.

Case, Continued

An ACE inhibitor is initiated and titrated to the maximally tolerated dosage. Three months later, her UACR is 210 mg/g. Her blood pressure is 128/76 mm Hg.

Additional laboratory test results:

eGFR = 56 mL/min per 1.73 m² (expected mild hemodynamic decline)
 Potassium = 4.7 mEq/L (SI: 4.7 mmol/L)
 Hemoglobin A_{1c} = 7.3% (56 mmol/mol)

Which of the following interventions would most effectively reduce her risk of CKD progression and cardiovascular events?

- A. Add an SGLT-2 inhibitor
- B. Initiate basal insulin to lower hemoglobin A_{1c} below 6.5% (<48 mmol/mol)
- C. Add a thiazolidinedione
- D. Discontinue ACE inhibitor due to eGFR decline
- E. Continue current therapy without additional changes

Answer: A) Add an SGLT-2 inhibitor

In patients with type 2 diabetes and CKD with albuminuria, SGLT-2 inhibitors (Answer A) significantly reduce progression to kidney failure, heart failure hospitalization, and cardiovascular events independent of glucose lowering.

The modest decline in eGFR after starting an ACE inhibitor is hemodynamically driven and expected. Discontinuing therapy (Answer D) reflects a common misinterpretation and a practice gap. Intensifying glycemic control alone (Answer B) does not provide comparable kidney protection. Thiazolidinediones (Answer C) do not improve kidney outcomes and may increase fluid retention. Continuing current therapy (Answer E) is not recommended, given the persistently high UACR, which is associated with both CKD progression risk and cardiovascular disease risk.

Case, Continued

The patient is started on an SGLT-2 inhibitor. Eighteen months later, UACR has decreased to 95 mg/g, and eGFR has stabilized at 55 mL/min per 1.73 m². She now presents with progressive exertional dyspnea and lower-extremity edema.

On physical examination, her blood pressure is 132/78 mm Hg, and pulse rate is 86 beats/min. She has bibasilar crackles on examination. There is 1+ bilateral ankle edema.

Current laboratory test results:

eGFR = 52 mL/min per 1.73 m²

N-terminal pro-B-type natriuretic peptide (NT-proBNP), elevated

Echocardiography shows a left ventricular ejection fraction of 38%.

Which of the following is the most appropriate next step to improve both heart failure and kidney outcomes?

- A. Discontinue the SGLT-2 inhibitor due to reduced eGFR
- B. Add a nonsteroidal MRA (eg, finerenone) with careful potassium monitoring
- C. Increase the metformin dosage
- D. Stop the ACE inhibitor to prevent further kidney decline
- E. Manage heart failure only; kidney-directed therapy is separate

Answer: B) Add a nonsteroidal MRA (eg, finerenone) with careful potassium monitoring

This patient now has heart failure with reduced ejection fraction (HFrEF) and persistent CKD with albuminuria. Nonsteroidal MRAs (Answer B) have been shown to slow the progression of kidney disease and reduce cardiovascular events in patients with diabetes and CKD, and mineralocorticoid receptor antagonism is foundational in HFrEF management.

Discontinuing the SGLT-2 inhibitor (Answer A) is inappropriate; these agents improve heart failure outcomes even at eGFR levels as low as 20 to 25 mL/min per 1.73 m². Stopping ACE inhibition (Answer D) would worsen both kidney and cardiovascular risks. Heart failure and kidney disease must be managed in an integrated fashion (Answer E). While continuing metformin is not contraindicated in this case, there is no evidence that increasing the metformin dosage (Answer C) would offer any benefit for heart failure.

Key Learning Points

- Note that albuminuria is an early, high-risk marker, even with eGFR ~60 mL/min per 1.73 m².
- Confirm persistence and stage of CKD using G and A categories.
- Initiate and titrate RAS blockade.
- Add an SGLT-2 inhibitor for organ protection independent of glycemia.
- Recognize expected hemodynamic eGFR changes.
- Integrate cardiovascular-kidney-metabolic therapy.
- Escalate therapy with MRAs when indicated.
- Avoid therapeutic inertia and misinterpretation of laboratory trends.

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Type 2 Diabetes in Preconception, Pregnancy, and Postpartum

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the essential components of preconception care for individuals living with type 2 diabetes.
- Recommend the best management approach for type 2 diabetes during pregnancy.
- Outline best practices for postpartum care for individuals living with type 2 diabetes.

Significance of the Clinical Problem

Historically, preexisting diabetes in pregnancy was predominantly due to type 1 diabetes, with type 2 diabetes constituting a smaller proportion. However, this landscape has changed dramatically over the past several decades.¹ Data from the United States reveal that the overall rate of pregestational diabetes was 10.9 per 1000 births in 2021, a 27% increase from 2016.² The observed increases in pregestational diabetes are driven predominantly by a sharp rise in the prevalence of type 2 diabetes, as exemplified by United Kingdom national data showing that it now accounts for two-thirds of all cases of pregestational diabetes.³ Underpinning this increase is the growing prevalence of obesity and type 2 diabetes among young people, which is highest in indigenous populations.⁴ Furthermore,

more people are becoming pregnant at advanced ages, and we may also be witnessing increased intergenerational transmission due to in utero exposure to hyperglycemia.¹

Maternal type 2 diabetes in pregnancy increases the risk of complications for both the mother and the child. A recent systematic review and meta-analysis found that compared with pregnancies unaffected by diabetes, those with maternal type 2 diabetes were more likely to have babies with congenital anomalies (odds ratio [OR] 1.76 [95% CI, 1.11-2.79]), large-for-gestational-age (OR 2.79 [95% CI, 1.93-4.04]), perinatal mortality (OR 4.18 [95% CI, 2.91-6.01]), and stillbirth (OR 7.27 [95% CI, 3.01-17.53]).⁵ In fact, compared with pregnancies affected by type 1 diabetes, those with type 2 diabetes were more likely to have small-for-gestational-age babies and to experience higher neonatal and perinatal mortality (OR 2.29 [95% CI, 1.12-4.67]; OR 1.53 [95% CI, 1.20-1.94]; and OR 1.31 [95% CI, 1.07-1.61], respectively).⁵

High-quality diabetes care before, during, and after pregnancy is therefore essential for improving clinical outcomes in this vulnerable population.

Practice Gaps

- Although preconception care is associated with improved pregnancy preparation and a lower risk of severe adverse pregnancy outcomes, most people with type 2 diabetes do not receive preconception counseling or care.

- Controversy surrounds the use of noninsulin glucose-lowering agents before, during, and after pregnancy, leaving clinicians unsure about the optimal approach.
- Suboptimal communication and transitions of care between obstetrics/gynecology, primary care, and specialists lead to missed opportunities for postpartum care and long-term risk reduction.

Discussion

Preconception

For people of reproductive age with type 2 diabetes, every clinical visit should incorporate screening for pregnancy intent.⁶ In addition, individuals with a history of gestational diabetes should undergo preconception screening for diabetes.⁷ If pregnancy is not desired, the use of effective contraception is strongly recommended. Long-acting reversible contraception is preferred, but the choice should be individualized, considering patient preference, comorbidities (including obesity and hypertension), concurrent treatments that might alter efficacy (eg, GLP-1 receptor agonists [GLP-1 RAs]), and the pregnancy timeline. The risk of most contraceptive options is lower than the risk of an unplanned pregnancy, and high-quality, online resources are available to guide clinicians in their recommendations.^{8,9}

Preconception care effectively improves pregnancy preparation and lowers the risk of congenital malformations.¹⁰⁻¹² The cost of delivering a structured prepregnancy care program is lower than the excess cost of managing adverse pregnancy outcomes among those who do not attend.¹⁰ The *Box* (following page) summarizes the key components of preconception care as outlined by the American Diabetes Association.⁷ Preconception care programs may be based in the community¹³ or in a specialty clinic,¹⁰ but should include access to a multidisciplinary care team, including an endocrinologist, maternal-fetal medicine specialist, dietician, and diabetes educator to optimize prepregnancy health as needed.¹⁴ Preconception care should be

delivered in a culturally sensitive, positive, and nonjudgmental manner. The risks associated with diabetes in pregnancy should be outlined, and patients should be supported in reducing these risks through glycemic goal setting, lifestyle interventions, and other medical interventions. Education on the physiological changes expected during pregnancy, including increasing insulin resistance and the need for more frequent outpatient follow-up, is essential.

Given the direct relationship between early-pregnancy maternal hyperglycemia and congenital malformations,¹⁵ it is recommended to achieve glucose levels as close to normal as safely possible, with a hemoglobin A_{1c} of less than 6.5% (<48 mmol/mol). The following glucose goals are recommended during the preconception period: preprandial glucose of 80 to 110 mg/dL (4.4-6.1 mmol/L) and 2-hour postprandial glucose less than 155 mg/dL (<8.6 mmol/L).⁷ Before pregnancy, it is necessary to discontinue potentially teratogenic medications, including GLP-1 RAs, SGLT-2 inhibitors, DPP-4 inhibitors, angiotensin receptor blockers, ACE inhibitors, and, in most cases, lipid-lowering therapies. Therefore, since sulfonylureas are no longer favored for use in pregnancy, periconceptual glucose-lowering pharmacotherapy centers on insulin and/or metformin. Due to their efficacy in weight reduction and glycemic control, GLP-1 RAs pose a challenge in this clinical setting, as evidence to guide optimal practice is lacking. Based on their half-life, it is accepted that semaglutide should be stopped 2 months before pregnancy and tirzepatide 1 month before pregnancy. We plan the timing of discontinuation for each individual, considering factors such as the likelihood of conception after discontinuing contraception, the drug formulation in use, and risks of prolonged time off the medication before pregnancy.⁶ For blood pressure control, pregnancy-safe options include labetalol, nifedipine, or methyldopa.

Screening for microvascular complications should include a physical examination, a dilated eye examination, measurement of serum creatinine, and a urine albumin-to-creatinine ratio

Box. Key Components of Preconception Care for People With Prediabetes, Diabetes, or a History of Gestational Diabetes

Preconception education should include: Comprehensive nutrition assessment and recommendations for: • Overweight and obesity or underweight • Meal planning • Correction of nutritional deficiencies • Caffeine intake • Safe food preparation technique Lifestyle recommendations for: • Regular moderate exercise • Avoidance of hyperthermia (hot tubs) • Adequate sleep Comprehensive diabetes self-management education Counseling on diabetes in pregnancy per current standards, including natural history of insulin resistance in pregnancy and postpartum; preconception glycemic goals; avoidance of diabetic ketoacidosis or severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy in individuals with preexisting diabetes; polycystic ovary syndrome (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, stillbirth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy Supplementation • Folic acid supplement (400-800 mcg daily routine) • Appropriate use of over-the-counter medications and supplements	Screening should include: Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs or symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine albumin-to-creatinine ratio Anemia Genetic carrier status (based on history): • Cystic fibrosis • Sickle cell anemia • Tay-Sachs disease • Thalassemia • Others if indicated Infectious disease
Health assessment and plan should include: • General evaluation of overall health • Evaluation of diabetes and its comorbidities and complications, including diabetic ketoacidosis or severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, metabolic dysfunction-associated steatotic liver disease, polycystic ovary syndrome, and thyroid dysfunction; complications such as macrovascular disease in individuals with preexisting diabetes, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy • Evaluation of obstetric or gynecologic history, including a history of cesarean delivery, congenital malformations, or fetal loss; current methods of contraception; hypertensive disorders of pregnancy; postpartum hemorrhage; preterm delivery; previous macrosomia; Rh incompatibility; and thrombotic events (deep vein thrombosis/pulmonary embolism) • Review of current medications and their appropriateness during pregnancy	Preconception plan should include: • Immunizations • Nutrition and medication plan to achieve glycemic goals before and appropriate) and pump technology (if indicated and appropriate) • Contraceptive plan to prevent pregnancy until glycemic goals are achieved • Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy, Rh incompatibility, and thyroid dysfunction

Reprinted from American Diabetes Association Professional Practice Committee for Diabetes. 15. Management of Diabetes in Pregnancy: Standards of Care in Diabetes-2026. *Diabetes Care*, 2026; 49(Supplement 1): S321-S338.

pregnancy. Folic acid supplementation (400-800 mcg daily)⁷ should be initiated at least 4 weeks before conception and continued until 12 weeks' gestation. A decision about whether to proceed with pregnancy in the setting of multiple comorbidities should involve careful discussion of anticipated maternal and fetal risks and the likelihood of a successful outcome.

Unfortunately, most eligible individuals with type 2 diabetes do not receive preconception counseling and care, and previous interventions have had a limited effect on care uptake.¹⁶ Future work should focus on addressing reported barriers to care. These barriers include low awareness among individuals with diabetes and professionals of the risks associated with type 2 diabetes in pregnancy and inefficient care processes.^{17,18}

in the year before pregnancy. If microvascular complications and additional comorbidities are present, they should be optimally treated before

Pregnancy

At Mayo Clinic, if diabetes has not already been diagnosed preconceptually, all pregnant people undergo screening for undiagnosed type 2 diabetes at their first prenatal visit. Type 2 diabetes is diagnosed when the early-pregnancy hemoglobin A_{1c} is 6.5% or higher (≥ 48 mmol/mol). While selective screening of individuals with risk factors can be considered,¹⁹ we find that a universal screening approach is more effective in our practice. Routine prenatal care should be delivered in accordance with institutional protocols, with additional emphasis on comprehensive diabetes care.¹⁴

The following glycemic goals are recommended once pregnancy is confirmed, with the lower limits only applicable if the individual is using insulin therapy:

- Fasting glucose: 70-95 mg/dL (3.9-5.3 mmol/L)
- 1-Hour postprandial glucose: 110-140 mg/dL (6.1-7.8 mmol/L) or
- 2-Hour postprandial glucose: 100-120 mg/dL (5.6-6.7 mmol/L)

Premeal testing is also recommended when using rapid-acting insulin to guide prandial dose adjustments. Either capillary glucose testing or continuous glucose monitoring (CGM) may be used to achieve these glycemic goals. To date, no clinical trials have demonstrated the efficacy of CGM over capillary glucose testing for pregnancy-specific outcomes in type 2 diabetes. However, the benefits of CGM observed outside of pregnancy (eg, reductions in hypoglycemia in those at risk) are expected to apply during pregnancy. When using CGM, individuals still need to pay close attention to fasting and postmeal glucose targets. The pregnancy-specific target range of 63 to 140 mg/dL (3.5-7.8 mmol/L) differs from the default device targets and must be manually adjusted. The optimal percentage of time-in-range for type 2 diabetes in pregnancy is not well defined, but a reasonable target is greater than 90% (compared with >70% in pregnancy with type 1 diabetes).²⁰ Hemoglobin A_{1c} should be monitored monthly, with a goal of less than

6.0% (<42 mmol/mol).⁷ Hypoglycemia thresholds include blood glucose less than 70 mg/dL (<3.9 mmol/L) and/or sensor glucose less than 63 mg/dL (<3.5 mmol/L).⁷ We relax these thresholds if the individual has a history of severe hypoglycemia or hypoglycemia unawareness. Compared with those with type 1 diabetes, individuals with type 2 diabetes are less likely to develop diabetic ketoacidosis. However, if diabetic ketoacidosis does occur, it is associated with increased fetal mortality.²¹ Therefore, clinicians should maintain a high index of suspicion, particularly in higher-risk situations such as use of exogenous glucocorticoids.²¹

While we await high-quality studies to guide optimal carbohydrate intake during pregnancy, we recommend 175 g per day. This allows 40 to 50 g per meal and 10 to 15 g per snack. A diet rich in whole foods (fruits, vegetables, whole grains, and lean proteins) is recommended, and intake of processed foods, fatty red meats, and sweetened foods should be restricted.⁷ We recommend total avoidance of sugar-sweetened beverages. A registered dietitian can be instrumental in guiding individuals toward positive dietary choices. Although individualized targets may be required, a general goal of 30 minutes of moderate-intensity physical activity (such as brisk walking) at least 5 days a week is advised.^{14,22} These lifestyle interventions improve glycemic control and support adherence to the Institute of Medicine guidelines for gestational weight gain (*Table*).²³

Table. Institute of Medicine Guidelines for Weight Gain During Pregnancy Based on Prepregnancy BMI

Pregestational BMI category	BMI, kg/m ²	Recommended total weight gain, kg
Underweight	<18.5	12.5-18.0
Normal weight	18.5-24.9	11.5-16.0
Overweight	25.0-29.9	7.0-11.5
Obese	≥ 30.0	5.0-9.0

Adapted from Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Rasmussen KM & Yaktine AL, eds. Washington (DC): National Academies Press (US); 2009.

Although not required preconceptually, most people with type 2 diabetes require insulin therapy during pregnancy, and insulin is the preferred agent for managing hyperglycemia. None of the commercially available insulins has been shown to cross the placenta. We typically use a multiple daily injection insulin regimen with rapid-acting insulin (eg, lispro, aspart, glulisine) and basal insulin (eg, glargine, degludec). Data on insulin pump use in type 2 diabetes during pregnancy are limited²⁴; however, this is expected to change with increasing use of technology and the approval of hybrid closed-loop insulin delivery systems for people with type 2 diabetes.²⁵ Mirroring recommendations for type 1 diabetes,⁶ if an individual with type 2 diabetes becomes pregnant while using an insulin pump, our approach is to use the hybrid closed-loop functionality (off-label) with workarounds to optimize glycemic control.²⁶ For this approach to be successful, the user must have access to expert advice from someone with an in-depth understanding of the hybrid closed-loop algorithm and the impact of pump setting adjustments on insulin delivery. Whether using injections or an insulin pump, the key to achieving and maintaining glycemic control during pregnancy is frequent insulin dose adjustments and understanding that bolus insulin requirements contribute a larger proportion of the total daily dose as pregnancy progresses. One benefit of electronic patient portals and cloud-based diabetes management platforms is the ability to provide individualized insulin dose adjustment advice 1 to 2 times per week (and more frequently if needed). In our practice at Mayo Clinic, this contact complements our formal visits, which are scheduled every 2 to 4 weeks either in person or via telehealth.

Metformin crosses the placenta,²⁷ and although it may reduce insulin requirements, weight gain, and cesarean delivery rates, it has been associated with an increased risk of small-for-gestational-age babies, particularly in the context of maternal hypertension or nephropathy.²⁸⁻³⁰ Our practice is to use metformin cautiously in lower-risk individuals and to avoid it in those with baseline

chronic hypertension or nephropathy. We also avoid the medication in individuals who likely have a significant insulin secretory defect (eg, those with a lower BMI, longstanding diabetes, or South and East Asian ancestry).

Pregnant individuals with type 2 diabetes should be prescribed aspirin (100-150 mg daily) starting at 12 to 16 weeks' gestation to lower the risk of preeclampsia. A blood pressure threshold of less than 140/90 mm Hg is recommended for initiating and titrating therapy.⁷ For patients with microvascular or macrovascular diabetes complications, close subspecialty follow-up is required throughout pregnancy. A dilated eye examination is advised in each trimester. A detailed fetal anatomy scan should be performed at 18 to 20 weeks' gestation, with further evaluation as needed.³¹ After 32 weeks, close monitoring, including ultrasound evaluation of fetal well-being, is advised.³¹ Shared decision-making about delivery timing is an essential part of routine obstetric care. Recent evidence and recommendations indicate that risk may outweigh the benefit of expectant management beyond 38 weeks' gestation in all cases of pregestational diabetes.⁶ Earlier induction should be considered in high-risk circumstances, such as poor glycemic control, previous stillbirth, or diabetes-related obstetric complications. During active labor and delivery, hourly glucose monitoring is recommended. Our approach is to target a glucose range of 70 to 110 mg/dL (3.9-6.1 mmol/L) and to initiate intravenous insulin if the individual is above goal.

Postpartum

Insulin sensitivity improves dramatically after delivery of the placenta, increasing the risk of hypoglycemia among those using exogenous insulin. Glycemic goals return to prepregnancy recommendations. It is helpful to document a tentative postpartum diabetes plan in the electronic medical record and discuss it with the patient in advance. Important components of postpartum care include contraceptive and pregnancy planning,

obesity care, lactation support, management of postpartum hypertension, screening for depression, and management of thyroid disorders.⁶ Individuals with preexisting diabetes have an increased risk of postpartum complications, including hypertension and sepsis,^{32,33} and are less likely to breastfeed.³⁴ Glycemic control tends to deteriorate postpartum, and lapses in diabetes care are common—20% at 12 months in a population-based study.³⁵ Because postpartum care often becomes preconception care, this is a critical time to support individuals with type 2 diabetes in achieving improved health and well-being. Strategies such as offering additional postpartum appointments, providing easier access to specialty care, and establishing clear transition pathways from obstetric care may be helpful. Individuals with significant risk factors for nonattendance (including low health literacy, transportation barriers, language barriers, and lack of insurance) may benefit from additional support, such as engagement with a designated health care worker.

Clinical Case Vignettes

Case 1

A 28-year-old woman is referred for urgent endocrine evaluation after an unexpected pregnancy is diagnosed. She is gravida 1, para 0, and ultrasonography estimates the gestational age to be 11 weeks and 2 days. She has obesity and a 2-year history of type 2 diabetes. Her current BMI is 38.4 kg/m². She has no diabetes-related complications or other comorbidities. Her blood pressure is 118/72 mm Hg. Her current medications include semaglutide, 2.4 mg once weekly (last dose 6 days ago), metformin, 1000 mg twice daily, and insulin glargine, 34 units at night. Her hemoglobin A_{1c} is 5.7% (39 mmol/mol). She uses a CGM, and fasting glucose values range from 80 to 95 mg/dL (4.4–5.3 mmol/L), with 2-hour postmeal values of 115 to 130 mg/dL (6.4–7.8 mmol/L). Although the pregnancy was unplanned, she is keen to proceed.

In addition to stopping semaglutide, which of the following should you recommend?

- A. Stop metformin
- B. Add glimepiride
- C. Start prandial insulin
- D. Advise termination of pregnancy
- E. Measure fructosamine

Answer: C) Start prandial insulin

This patient has postprandial glucose values above the desired range for pregnancy and is likely to experience significant deterioration in prandial glycemic control as the effect of semaglutide wears off. Therefore, she should be prescribed prandial insulin (Answer C). In this case, since the glucose values are only modestly elevated, one could start with approximately 12 units before meals, with education on the anticipated need to up-titrate over the coming days and weeks. A recent large retrospective cohort study confirms clinical practice observations that previous GLP-1 RA use with discontinuation for pregnancy is associated with greater gestational weight gain.³⁶ Discontinuation of metformin (Answer A) may exacerbate this issue, and since this patient has no comorbidities, it is reasonable to continue at this time. She will benefit from medical nutrition therapy and a structured exercise program to prevent rebound weight gain. Glimepiride (Answer B) is no longer preferred for the treatment of type 2 diabetes in pregnancy because it crosses the placenta, is associated with an increased risk of neonatal hypoglycemia, and long-term offspring safety data are not available.⁷ Although animal studies and some human case reports raise concern for an increased risk of congenital malformations in GLP-1 RA–exposed offspring, recent large observational studies do not confirm this.^{36,37} These data provide some reassurance to those who become pregnant while using this class of medications, and although it is prudent to stop the medication, it is not routine practice to advise termination (Answer D) when this situation arises. Although gestational changes in red blood cell turnover make hemoglobin A_{1c}

less reliable in pregnancy, it is widely available, and increases are associated with adverse pregnancy outcomes. Fructosamine (Answer E), an alternative biochemical marker of glycemia, does not enhance the prediction of pregnancy outcomes compared to hemoglobin A_{1c} and is not preferred. In any case, additional glycemic metrics are not needed before adding prandial insulin in this scenario.

Case 2

A 41-year-old pregnant woman originally from South Asia (gravida 4, para 1) presents for follow-up. She is 30 weeks' gestation and has lived with type 2 diabetes for 18 years. She previously developed gastrointestinal adverse effects with metformin and GLP-1 RA–based therapies and transitioned to hybrid closed-loop insulin pump therapy 5 years ago. She has background diabetic retinopathy. Her BMI is 28 kg/m², and her gestational weight gain has been at the lower end of the recommended range. On her current regimen, she uses an average of 140 units of insulin aspart per day, 65% of which is bolus insulin. She continues to use her pump's automated mode. Her hemoglobin A_{1c} was 6.1% (43 mmol/mol) 1 week ago, and her time-in-pregnancy target range is 78% with 4% in time-below-range. She reports being very frustrated with her glycemic control, noting that even when she boluses 15 minutes before meals as recommended, her glucose spikes and then rapidly drops 3 to 4 hours later, often requiring treatment for hypoglycemia.

Which of the following should you recommend?

- A. Switch to U500 insulin
- B. Have a protein snack after meals
- C. Change the pump to manual mode
- D. Bolus 30 minutes before eating
- E. Restrict carbohydrates to 30 g per meal

Answer D) Bolus 30 minutes before eating

A common challenge in managing insulin-requiring diabetes during pregnancy is postprandial hyperglycemia at 1 to 2 hours, followed by hypoglycemia 3 to 4 hours after eating. This pattern results from a delay in the peak postprandial insulin concentration and increased peripheral insulin resistance as pregnancy progresses.³⁸ It is therefore recommended to inject prandial insulin 15 minutes before meals in early pregnancy and 30 to 40 minutes before meals in late pregnancy (Answer D). An additional strategy is to reduce sugar intake and incorporate more complex carbohydrates with each meal. Because of its action profile, which is quite different from that of U100 insulin (resembling intermediate-acting insulin), U500 insulin (Answer A) is rarely used during pregnancy. Rapid-acting U200 insulin's pharmacodynamic profiles, however, are bioequivalent to U100 formulations and can help reduce the total volume of insulin injected and the frequency of infusion set changes in people with higher insulin requirements. It is important that the use of concentrated insulin be clearly marked in the patient's medical record and on their pump, and that this be considered when making changes to insulin pump settings (as the pumps are designed for U100 insulin only). Although additional protein intake (Answer B) can reduce the risk of hypoglycemia, this reactive approach is less favorable than treating the underlying problem: a mismatch between insulin and the timing of meals. Changing the pump to manual mode (Answer C) could exacerbate this problem, as the patient would lose the benefit of automated basal insulin suspension. Excessive carbohydrate restriction (Answer E) could be harmful and is not recommended.

Case 3

A 32-year-old pregnant woman (gravida 3, para 2) presents at 36 weeks and 5 days' gestation for diabetes evaluation. Labor induction is planned for the following week. She was diagnosed with type 2 diabetes after her previous pregnancy and was prescribed metformin, 1000 mg twice daily,

but did not take it consistently. Her hemoglobin A_{1c} was 8.4% (68 mmol/mol) at her first prenatal visit (10 weeks' gestation) and is now 5.9% (41 mmol/mol) on insulin glargine, 52 units once daily, and insulin aspart, 34 units before meals. She plans to breastfeed and is eager to lose weight postpartum.

Which of the following should you recommend immediately postpartum?

- A. Metformin, 500 mg with the evening meal, and insulin glargine, 30 units before bed
- B. Insulin glargine, 20 units before bed, and insulin aspart, 10 units before meals
- C. Metformin, 500 mg with the evening meal, and tirzepatide, 2.5 mg once weekly
- D. Correction-scale insulin before meals and bedtime
- E. Insulin glargine, 37 units before bed, and insulin aspart 24 units before meals

Answer B) Insulin glargine, 20 units before bed, and insulin aspart, 10 units before meals

Our typical approach is to reduce prepregnancy and early-pregnancy insulin doses (both basal and bolus) by 30% and recommend this as a postpartum starting point. However, when prepregnancy insulin requirements are unknown or glycemic control was suboptimal in early pregnancy, it is reasonable to recommend one-third to one-half of predelivery doses (Answer B).³¹ Because postpartum recommendations are typically crude estimates of actual requirements, it is most important to ensure close glycemic monitoring and patient awareness of the risk of

both hypoglycemia and hyperglycemia. GLP-1 RA-based therapies (Answer C) are unsuitable for breastfeeding because of the lack of safety data and theoretical concerns that the associated appetite suppression and weight loss may affect milk supply. Metformin and basal insulin (Answer A) may be an option for this patient in the future. However, metformin takes several days to begin affecting blood glucose concentrations, and we typically wait 3 to 4 days postpartum to reinstitute it to optimize tolerance. The use of correction-scale insulin (Answer D) is a reactive approach and would not achieve optimal glycemic control in this patient, who has required more than 150 units of insulin per day during pregnancy. Answer E provides insulin doses that are merely a 30% reduction from predelivery doses and could cause hypoglycemia.

Key Learning Points

- Individuals with type 2 diabetes experience adverse pregnancy outcomes similar to those of individuals with type 1 diabetes.
- Screening for pregnancy intent and prepregnancy care is vital for individuals with type 2 diabetes and can improve the likelihood of optimal pregnancy outcomes.
- Insulin is the preferred pharmacotherapy for type 2 diabetes in pregnancy.
- A clearly documented management plan supports safe and effective glycemic management during the postpartum transition.

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Transition of Care in Patients With Youth-Onset Type 2 Diabetes

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify the unique characteristics of youth-onset type 2 diabetes (yo-T2D) that affect transition of care from pediatric to adult endocrinology.
 - Use effective receivership approaches to better receive, maintain, and care for this high-risk population.
 - Provide important preconception counseling to young adults.
-

Significance of the Clinical Problem

T2D, once called “adult-onset diabetes,” has steadily increased in prevalence among children and adolescents in the United States and globally, becoming an emerging epidemic with serious long-term implications. yo-T2D, defined as T2D diagnosed in people younger than 20 years, has an aggressive clinical course and higher rates of long-term complications. Because yo-T2D typically presents during adolescence and emerging adulthood, effective long-term management depends on the successful transition of care from pediatric to adult health care systems. As the number of young adults with yo-T2D continues

to grow, ensuring that clinicians are prepared to care for this unique and complex population is increasingly critical.

Practice Gaps

- Emerging adults with yo-T2D are at high risk for worsening glycemic control and gaps in clinical care.
- Most programs and research on diabetes health care transition (HCT) focus on patients with type 1 diabetes (T1D).
- Despite significant improvements in overall diabetes complication rates, yo-T2D has high rates of complications within 10 years of diagnosis, when patients are only in their mid-20s.

Discussion

Youth-Onset Type 2 Diabetes

The prevalence of yo-T2D has doubled over the past 20 years. In the SEARCH for Diabetes in Youth Study, prevalence increased from 0.34 per 1000 youths in 2001 to 0.67 per 1000 in 2017, a 95% relative increase over 16 years.¹ This increase varies significantly among racial and ethnic groups, with the highest burden seen among Black and Native American youths at a prevalence of 1.8 and 1.63 per 1000, respectively. Although the overall population prevalence of yo-T2D remains lower

than that of T1D at 2.15 per 1000 youths, in Native Americans, yo-T2D diagnoses already outnumber those of T1D (0.56 cases per 1000). This trend has been observed globally, with T2D incidence among 15- to 24-year-olds rising from 56 per 100,000 to 123.9 per 100,000 from 1990 to 2021.² As this population continues to grow and age, it is critical that clinicians are prepared to care for them.

yo-T2D differs fundamentally from both childhood-onset T1D and adult-onset T2D. It is characterized by reduced insulin sensitivity, an initial phase of β -cell hypersecretion followed by rapid β -cell decline, and accelerated development of complications.³⁻⁵ In early management of yo-T2D, lifestyle alone is inadequate as primary therapy. Initial treatment focuses on metformin, with or without basal insulin, based on hemoglobin A_{1c} at diagnosis and the presence of diabetic ketoacidosis. Once hyperglycemia has improved, some individuals with yo-T2D achieve glycemic control on metformin alone; however, this control is tenuous, and decompensation requiring therapy escalation is common. Achieving adequate control is complicated by significant insulin resistance, and insulin doses higher than 1 unit/kg per day may be required. A growing number of incretin-based therapies and SGLT-2 inhibitors are now approved and used in adolescents; however, inadequate access, poor adherence, variable response rates, and lack of long-term outcome data remain important challenges.⁶

The nuances of yo-T2D care extend beyond treatment during adolescence into adulthood. Complication rates are higher in yo-T2D than in both T1D and later-onset T2D.^{7,8} Long-term follow-up from the TODAY study (Treatment Options for Type 2 Diabetes in Adolescents and Youth) showed that 60.1% of participants developed at least 1 microvascular complication by their mid-20s, and 28.4% had 2 or more.⁹ Thus, most emerging adults with yo-T2D develop a complication before their third decade of life. Given the high risk of complications and the relatively low risk of hypoglycemia, a hemoglobin A_{1c} target of less than 6.5% (<48 mmol/mol) is recommended for patients with yo-T2D.¹⁰ The challenge then is to maintain this tight control through the transitions in a young adult's life.

Transitions in Health Care

The transition from pediatric to adult health care systems, or HCT, is a period of significant transformation and turbulence in an emerging adult's life. In addition to changes in school, work, personal life, living situations, finances, and insurance, emerging adults assume greater responsibility and autonomy across all aspects of their lives, including their health. At this time, emerging adults move from a pediatric system, which is family-focused and provides significant support, to an adult health care system that emphasizes the individual patient and personal responsibility. Combined with the loss of long-held relationships with the pediatric health care team and decreased support from their own families, HCT can be a significant challenge for many young adults.

For individuals with diabetes, HCT is associated with glycemic deterioration, gaps in care, increased complications, and psychosocial challenges.⁶ Structured HCT programs have been developed to counter these poor outcomes and have demonstrated improved follow-up, fewer hospitalizations, and modest improvements in glycemic control.^{6,11} While this work on diabetes transitions is encouraging, most HCT research focuses on T1D. Only 12% of diabetes HCT research includes yo-T2D, and just 2% focuses exclusively on yo-T2D.¹² Among studies specifically examining yo-T2D, undergoing HCT is associated with a higher odds of hemoglobin A_{1c} values greater than 9.0% (>75 mmol/mol) compared with hemoglobin A_{1c} among those who remain with pediatric providers.¹³ Insurance coverage significantly influences access to care after transition. States with expanded Medicaid have improved follow-up, although insurance type does not affect hemoglobin A_{1c}.¹⁴ Notably, even when insurance is not a barrier, individuals with yo-T2D have lower follow-up rates than those with T1D.¹⁵ Qualitative work exploring the illness experiences of emerging adults before and after transition highlights the importance of addressing mental health needs, strengthening organizational skills, and identifying support persons to facilitate

ongoing care.¹⁶ Despite the collective work and interest to date, there are no controlled studies evaluating the effectiveness of structured HCT programs for young adults with yo-T2D.

Barriers

As we consider how best to transition the care of young adults with yo-T2D, several key challenges must be recognized and addressed. As previously discussed, yo-T2D has an aggressive phenotype and poses significant challenges in achieving glycemic control. While the goal is stable glycemic control before and throughout HCT, this is not a reality for many transitioning young adults. yo-T2D is associated with lower socioeconomic status and disproportionately affects youth from historically marginalized communities.¹⁷ These factors often translate into reduced family financial support, fewer opportunities for higher-paying jobs that include insurance upon entering adulthood, and greater systemic barriers to navigating the adult health care system. Emerging adults with yo-T2D are frequently in a precarious position at the time of HCT, with higher rates of government insurance or no insurance. This leaves them particularly vulnerable to gaps in insurance coverage. Although private insurance now covers dependents through age 26, this coverage relies on the parent or guardian having private insurance. Pediatric Medicaid only covers young adults through age 18. This gap can leave emerging adults uninsured or underemployed to maintain eligibility for government insurance. Underemployment early in adulthood can affect lifelong earning potential and increase the long-term financial burden of T2D. Without adequate insurance, the costs of insulin, incretin-based therapies, and SGLT-2 inhibitors can be crippling. Finally, yo-T2D occupies a unique position as a pediatric specialist's disease, while also being common in adulthood. It is often challenging for emerging adults to book appointments with endocrinologists and diabetologists for more intensive monitoring and management due to the lack of clear recognition of yo-T2D as a

disease that warrants special attention from the medical community.

Despite these challenges, there is considerable hope for yo-T2D HCT. Diabetes care has rapidly evolved over the past 2 decades, driven by advances in therapies and technologies. Incretin-based medications, in particular, provide good glycemic control, reduce complication rates, and aid in weight management, all in a single medication administered weekly, which can be critical for adherence among busy young adults. Technologies such as continuous glucose monitors and insulin pumps, once used exclusively for T1D management, now have expanded indications for T2D management.¹⁸ Finally, growing attention to both yo-T2D and HCT, as a whole, has revolutionized the conversation about caring for young adults and created opportunities for improved education, ongoing research, and systems improvement efforts that will continue to enhance the care of this unique population.

Clinical Case Vignettes

Case 1

An 18-year-old woman with yo-T2D presents to the pediatric diabetes clinic for follow-up of her diabetes. T2D was diagnosed at age 16 years. Her current management includes insulin glargine, 60 units daily; empagliflozin, 25 mg daily; metformin, 2000 mg daily; and dulaglutide, 4.5 mg weekly.

On physical examination, her blood pressure is 118/65 mm Hg, pulse rate is 72 beats/min, and temperature is 98.2°F (36.8°C). Her height is 63 in (160 cm), and weight is 165 lb (74.8 kg) (BMI = 29.2 kg/m²). She has grade 2 acanthosis nigricans on her neck.

Laboratory test results:

Hemoglobin A_{1c} = 6.9% (52 mmol/mol)
 Urinary albumin, normal
 AST = 45 U/L (SI: 0.75 μ kat/L)
 ALT = 60 U/L (SI: 1.00 μ kat/L)
 Complete metabolic panel, normal
 Complete blood cell count, normal

Overall, she feels well and has no history of hypoglycemia.

Based on her treatment regimen and lab values, which of the following is the best next step for management?

- A. Hemoglobin A_{1c} is at goal; continue current regimen without changes
- B. Hemoglobin A_{1c} is at goal; slowly wean insulin as able
- C. Hemoglobin A_{1c} is not at goal; increase insulin to target A_{1c} <6.5% (<48 mmol/mol)
- D. Hemoglobin A_{1c} is not at goal; transition to a stronger incretin-based therapy to target A_{1c} <6.5% (<48 mmol/mol)
- E. Hemoglobin A_{1c} is not at goal; add a sulfonylurea to target mealtime glucose

Answer: D) Hemoglobin A_{1c} is not at goal; transition to a stronger incretin-based therapy to target A_{1c} <6.5% (<48 mmol/mol)

Aggressive management of yo-T2D is recommended to prevent long-term complications with a target hemoglobin A_{1c} value of less than 6.5% (<48 mmol/mol).⁶ Because she is not experiencing hypoglycemia, further escalation of her regimen is reasonable. Considering her BMI and elevated AST and ALT, increasing the incretin-based therapy could provide additional weight loss. The highest available dosage of dulaglutide is 4.5 mg weekly. However, switching to semaglutide or tirzepatide could potentially achieve additional weight loss and glucose-lowering effects. Increasing incretin-based therapies is recommended over increasing insulin and adding a sulfonylurea because of the lack of secondary benefits, the risk of additional weight gain, and concerns about accelerated β -cell dysfunction with sulfonylureas.

Deescalation of therapy would not be recommended, as she is not experiencing hypoglycemia, and a more stringent target of less than 6.5% (<48 mmol/mol) is recommended for yo-T2D.

Case 1, Continued

Which of the following is the most appropriate approach to transitioning this patient to adult care?

- A. Plan to transfer to adult practice immediately, as she is now an adult and should no longer receive care at the children's hospital
- B. Begin HCT preparation now (if not started already); discuss HCT, including clinic expectations, patient preference, and goals, before transferring to the new clinic
- C. Delay HCT until 21 years old to minimize disruption at an age with significant changes; start discussing HCT 1 year before planned transfer
- D. Allow the patient the autonomy to initiate the conversation about when she is ready to transfer out of the clinic; since she is now an adult, you want to support her decision-making
- E. HCT planning and referral to an adult specialist should be the responsibility of her primary care provider; tell her to discuss with her primary care provider and give her 6 months of refills

Answer: B) Begin HCT preparation now (if not started already); discuss HCT, including clinic expectations, patient preference, and goals, before transferring to the new clinic

Planning and Implementing HCT Policy

HCT is a process, not just an event. The process should begin at least 1 year before transfer, ideally earlier, and for patients diagnosed at a younger age, it can begin in early adolescence.⁶ Clinics can use the Six Core Elements from Got Transition (Policy Creation, Tracking/Monitoring, Readiness Assessment/Education, Planning, Transfer of Care, and Transition Completion) to develop an approach. Patient education should include diabetes-specific training and age-appropriate health discussions, a graduated approach to patient autonomy, and discussions of insurance,

pharmacies, and how to interact with clinics and the health care system. Health discussions should include fertility counseling and the effects of drugs and alcohol on diabetes, with particular emphasis on the risks of alcohol for those on insulin. There is no age-specific cutoff for transfer, as it depends on the patient's needs and the capacity and strengths of the systems. It is not recommended to wait until patients initiate the conversation, as this causes variability and delays preparation. Care disruptions are common among patients in this age range due to changes in housing, employment, and insurance, so education should include troubleshooting and system navigation to best equip young adults to handle these challenges. The *Table* describes an approach to HCT for pediatric and adult clinics.

Equally important to preparing pediatric patients for HCT is ensuring that adult clinics are equipped to receive these young adults and maintain them as patients. The focus should be on key elements of effective receivership: openly communicating with pediatric colleagues, designating a coordinator

to assist with transferring patients, prioritizing relationships over hemoglobin A_{1c}, addressing psychosocial needs, and maintaining a team-based approach in the clinic.^{19,20} Even simple changes to clinic flow, such as recognizing yo-T2D as a target population for new patient slots and proactively building a welcoming environment with clear patient expectations, can improve access and care.

A unique aspect of HCT for yo-T2D is the ability to transition diabetes management to a primary care provider rather than to a subspecialist. Both approaches can be appropriate if the receiving clinician is familiar with yo-T2D and can provide adequate support. Decisions about the receiving provider should be individualized based on factors such as geography, provider availability and expertise, patient preference, and the level of diabetes complexity. Ultimately, creating a community of competent, invested health care professionals who are interested in and able to care for patients with yo-T2D as they enter adulthood provides the best environment for HCT.

Table. Approach to HCT for Pediatric and Adult Clinics

Pediatric preparation	Adult care engagement
Preparing youth for transfer	Supporting young adults in your practice
Develop a process • Create clinic policy • Distribute policy to patients and families • Build relationships with adult clinics (both primary care and specialists)	Develop a process • Make space in clinic for yo-T2D • Have clear process for referring clinics and new patients • Build relationships with pediatric clinics
Prepare patients • Education: ◦ Diabetes-specific ◦ Fertility planning, substance use ◦ Self-management skills ◦ System navigation • Address psychosocial needs • Obtain internal medicine/family medicine primary care provider	Receive patients • Welcome patient to the clinic • Provide introduction on how clinic works (refills, scheduling appointments, emergency line, etc) • Evaluate gaps in knowledge and management; provide education • Focus on relationship, not A_{1c}
Transfer patients • Refer patients • Prepare transfer letter/comprehensive summary note • Provide adequate refills • Follow-up to ensure attended first visit	Ongoing management and follow-up • Aggressive monitoring and management of comorbidities • Maintain tight glucose control with target A_{1c} <6.5% (<48 mmol/mol) • Have resources to address insurance and psychosocial needs

Case 2

A 19-year-old woman with yo-T2D is seeing you in clinic for diabetes follow-up, accompanied by her new husband. She was diagnosed with yo-T2D at age 11 years, and her care has been complicated by poor adherence and significant insulin resistance. Current medications include metformin ER, 2000 mg daily; insulin glargine, 75 units daily; and dulaglutide, 1.5 mg weekly. She misses about 2 insulin doses per week.

On physical examination, she appears well. Her blood pressure is 112/70 mm Hg, pulse rate is 78 beats/min, and temperature is 97.5°F (36.4°C). Her height is 66 in (168 cm), weight is 163 lb (74 kg) (BMI = 26.3 kg/m²).

Her hemoglobin A_{1c} is 12% (108 mmol/mol).

In addition to troubleshooting barriers to care, escalating her diabetes medication management, and discussing plans for HCT, what other topic of diabetes management and control is critical to review at this visit?

- Review diet and activity; emphasize healthy, whole foods; recommend at least 150 min/week of moderate to vigorous activity and strength training 3 days/week
- Discuss symptoms and management of hypoglycemia; the insulin dose needs to be increased at this time with possible addition of mealtime insulin; emphasize that understanding hypoglycemia is important to remain safe
- Review long-term outcomes and complications of poorly controlled T2D; she is at high risk of complications, and will improve her adherence if she is more aware
- Review symptoms and management of diabetic ketoacidosis; while less common in T2D than in T1D, it is still a complication that can occur in the setting of poor glycemic control
- Discuss prevention of unintended pregnancy and appropriate planning for intended pregnancy with goal hemoglobin A_{1c} <6.5% (<48 mmol/mol) while on medications that are not contraindicated in pregnancy

Answer: E) Discuss prevention of unintended pregnancy and appropriate planning for intended pregnancy with goal hemoglobin A_{1c} <6.5% (<48 mmol/mol) while on medications that are not contraindicated in pregnancy

While many of the listed topics could be beneficial, preconception counseling and planning are critical. Pregnancy prevention and planning should be addressed at puberty and revisited at every appointment, according to the recent Endocrine Society/European Endocrine Society guidelines on preexisting diabetes in pregnancy.²² Counseling should evolve with age. Although the conversation with teenagers often focuses on preventing unintended pregnancy, in emerging adults, counseling should also include planning for healthy pregnancies. For this patient, even though this topic has likely been discussed previously, ongoing counseling is critical.

Case 2, Continued

The patient agrees to the plan and counseling and reports that she is reliably using combined oral contraceptives. Two weeks after the visit, she contacts the clinic and lets you know she missed her period last week and had a positive pregnancy test today.

What immediate changes are needed for her regimen?

- No change in medications; you already increased everything 2 weeks ago; give additional time to ensure overtreatment does not occur
- Refer to maternal–fetal medicine obstetrician; make no changes until they can take over diabetes management
- Stop dulaglutide, continue metformin, continue basal insulin, and start short-acting insulin; rapid titration of insulin is necessary to achieve glucose control as soon as possible
- Stop dulaglutide; wait until a viability scan at 8 weeks to make any additional changes
- Start insulin pump therapy with an automated insulin delivery system

Answer: C) Stop dulaglutide, continue metformin, continue basal insulin, and start short-acting insulin; rapid titration of insulin is necessary to achieve glucose control as soon as possible

yo-T2D has a female predominance, with some studies reporting that 65% to 70% of those diagnosed in youth are female. Given this sex ratio, a major component of yo-T2D management in emerging adults is anticipating and preparing for pregnancy. In numerous studies following yo-T2D outcomes and transition in care, high rates of unintended pregnancy and major adverse complications are noted.^{15,21} According to an analysis of 452 young women with yo-T2D in the TODAY study, 10.2% became pregnant with a 20% rate of congenital anomalies.²³ A 20% rate of congenital anomalies is tragically high, and work is needed to reduce and prevent these adverse outcomes. While significant effort is made to warn against pregnancy throughout adolescence, upon reaching adulthood, pregnancy counseling should extend beyond advising against pregnancy and focus on patients' reproductive goals and what to do in the event of pregnancy. Proactive planning should aim for a hemoglobin A_{1c} value of less than 6.5% (<48 mmol/mol), with other comorbidities managed on a pregnancy-safe regimen for at least 3 months before conception. Contraception should be used until ready to conceive. At a minimum, low-dosage estrogen-containing oral contraceptive pills or progestin alone (eg, drospirenone) should be offered until long-acting reversible contraception is available. A family planning visit should be offered, given the high prevalence of unwanted pregnancies and adverse pregnancy outcomes. Preconception counseling and contraception decrease major malformations by 70%, perinatal mortality by more than 50%, and neonatal intensive care unit admissions by 25%.²⁴ For those with a hemoglobin A_{1c} value of less than 6.5% (<48 mmol/mol) before conception, malformation rates resemble those in populations without diabetes.

In addition to counseling on preconception goals, the importance of informing the clinic immediately after a positive pregnancy test should

be discussed. Emerging adults with T2D often take medications that should be stopped before pregnancy, such as incretin-based therapies and SGLT-2 inhibitors, for which data in pregnancy are limited. The mainstay of treatment in pregnancy is aggressive basal-bolus therapy with long- and rapid-acting insulin, and most patients with yo-T2D have little to no experience with this. Ideally, the diabetes medication regimen should be changed before attempting conception; however, if timing is less than ideal, treatment should shift to a basal-bolus insulin regimen as soon as possible. Metformin may be continued until the end of the first trimester. Because organogenesis occurs during the first 8 weeks, and major malformations cannot be prevented after that period, early optimization of glucose levels is critical and should occur before the first obstetric visit.

For this patient, referral to maternal–fetal medicine is recommended, but not for initial glucose management, as that would delay improvements in glycemic control and miss a critical stage of development. She is not on a regimen safe for pregnancy, so recommending no change in her medications is incorrect. Insulin pumps can be useful, but they are not an instant solution for glycemic control and should be started before pregnancy in interested patients, as they require significant knowledge and training to use appropriately.

Case 3

A 24-year-old man with yo-T2D presents to your clinic to establish care. He was diagnosed with T2D at age 14 years. He was initially started on metformin but required the addition of insulin for glycemic control. He was previously followed for diabetes at the children's hospital and at another adult endocrinology practice. He has been without follow-up care for 3 years. His current regimen is insulin glargine and insulin aspart (fixed-meal dosing), which was restarted during hospitalization for diabetic ketoacidosis a few months ago.

On physical examination, his blood pressure is 142/81 mm Hg, and pulse rate is 111 beats/min. His height is 66 in (167.6 cm), and weight is 247 lb (112 kg) (BMI = 39.9 kg/m²).

Laboratory test results:

Hemoglobin A_{1c} = 9.4% (79 mmol/mol)
 Urinary albumin/creatinine ratio = 4623.8 mg/g
 Creatinine = 0.72 mg/dL (SI: 63.6 μmol/L)
 T1D antibodies (GAD, IA-2, ZnT8), negative

What is the most important aspect of his care to focus on first at this initial visit?

- A. Improving his hemoglobin A_{1c}; he is at high risk for complication progression, and a target of <6.5% (<48 mmol/mol) is recommended for his age
- B. Understanding and addressing the barriers to follow-up that he has experienced for the last 3 years
- C. Weight management; given his elevated BMI and comorbidities, he should consider bariatric surgery
- D. Referral to nephrology given his albumin-to-creatinine ratio; don't be fooled by his low creatinine, as hyperfiltration can be an early sign of diabetic kidney disease
- E. Fast-track for insulin pump training and initiation; hybrid closed-loop systems are approved for T2D management

Answer: B) Understanding and addressing the barriers to follow-up that he has experienced for the last 3 years

Initial visits with complex patients are always a challenge in prioritization. The priority at this visit should be to establish rapport and troubleshoot barriers to follow-up. The remaining answers are all topics that should be managed or at least considered during his future visits. As discussed, his hemoglobin A_{1c} target should be lower, with a goal of tight glycemic control to reduce the risk of complications. Despite a normal creatinine value, severely increased albuminuria indicates early glomerular damage. In his case, hyperfiltration may lead to a lower creatinine value but be evidence of diabetic kidney disease.²⁵

Both bariatric surgery and insulin pumps with automated insulin delivery systems have shown promise for improving care in type 2 diabetes. Early use of bariatric surgery may be associated with higher rates of diabetes remission.²⁶ Insulin pumps with automated insulin delivery systems improve hemoglobin A_{1c} and time-in-range and are now approved for the management of T2D.¹⁸ Depending on his needs at future visits, both management strategies can be considered. In addition to the listed answers, several other aspects of screening and management need to be addressed in his diabetes care over time. Diabetes-related complications develop in most individuals with yo-T2D in their 20s. Given that he already has evidence of diabetic kidney disease, he is at high risk for retinopathy and neuropathy. His blood pressure is elevated and should be managed aggressively, with a target below 120/80 mm Hg. Lastly, comorbidities associated with metabolic syndrome and obesity should be addressed, including a sleep study to assess for obstructive sleep apnea, screening for metabolic dysfunction-associated steatotic liver disease, and lipid assessment and management.

The list of issues that need to be addressed in those with yo-T2D is long. It is easy to try to tackle everything at once, which can overwhelm patients already struggling with adherence and follow-up. The goal of this visit is to build rapport, provide support, encourage him to return to the clinic, and begin addressing all aspects of his diabetes care.

Key Learning Points

- yo-T2D differs fundamentally from both T1D and adult-onset T2D, with a more aggressive clinical course and higher rates of long-term complications.
- The transition period is marked by significant challenges, creating a “perfect storm” of biologic and health care system changes that worsen glycemic control, accelerate

complications, and result in high rates of care gaps.

- Additional research is needed to identify the most effective interventions to improve HCT in yo-T2D.
- Special attention should be given to preconception counseling and pregnancy

planning for young women with yo-T2D, starting at puberty.

- Many online resources are available to improve HCT, including GotTransition.org and the Endocrine Society's Transitions of Care section.

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Use of Adjunctive Glucose-Lowering Therapies to Target Cardiometabolic Risk in Type 1 Diabetes

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the pathophysiological mechanisms that contribute to increased cardiovascular (CV) risk in people with type 1 diabetes (T1D).
- Identify type 2 diabetes (T2D) medications that may be beneficial as adjunctive cardiometabolic agents in individuals with T1D.
- Safely manage patients with T1D who start off-label adjunctive cardiometabolic agents.

Significance of the Clinical Problem

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in adults with T1D¹ and occurs at a younger age than in those with T2D.² CVD risk factors, which vary with age and duration of T1D, include hyperglycemia (related to insulin deficiency and insulin resistance), hypertension, kidney disease, dyslipidemia, obesity, and smoking.³ Although not discussed in detail here, antihypertensive and LDL cholesterol-lowering medications confer CVD benefit in people with diabetes, although more studies have focused on T2D than on T1D. Statins have been shown to reduce lipids equally in T1D and T2D. In

the Heart Protection Study, the reduction in CVD events among 615 adults with T1D compared with 5348 adults with T2D was not significantly different, although the confidence intervals were wide.⁴ The Endocrine Society guideline, Lipid Management in Patients with Endocrine Disorders, made a conditional recommendation to initiate statin therapy irrespective of CV risk score in adults with T1D aged 40 years and older with a 20-year duration of diabetes and/or microvascular complications.⁵

This chapter focuses on medications that improve glycemic control and specifically target CVD outcomes in T1D.

Beyond insulin deficiency, insulin resistance is an underrecognized and undertreated CV risk factor in this population (*Figure 1, following page*).⁶ Insulin resistance is present in adolescents⁷ and adults^{8,9} living with T1D. It is induced, in part, by nonphysiological insulin delivery via the subcutaneous route, which results in portal hypoinsulinemia and peripheral hyperinsulinemia, thereby disrupting the normal balance of insulin exposure between the liver and peripheral tissues.¹⁰ Peripheral hyperinsulinemia is associated with weight gain,¹¹ which compounds insulin resistance, and with impaired glucose disposal, inappropriate free fatty acid release, GH hypersecretion (due to low IGF-1), and amplification of prandial glucagon secretion due to inadequate insulin exposure to hepatic tissue and pancreatic α -cells (*Figure 1*).¹²⁻¹⁵

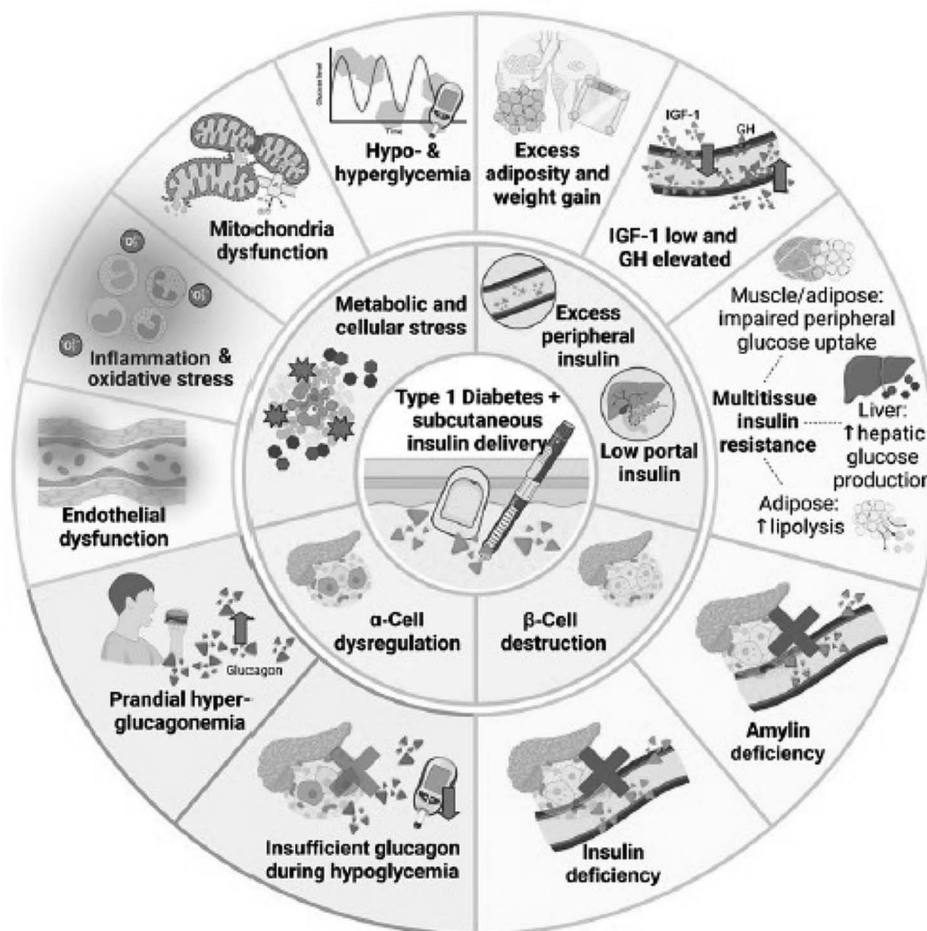
These defects combine to increase CV risk in T1D^{14,16} and are potential therapeutic targets to improve CV outcomes.¹⁷

Inflammation is a potential link among insulin resistance, atherothrombosis, and ischemic heart disease.¹⁸ Insulin resistance increases the production of proinflammatory cytokines, which can further impair insulin signaling.¹⁹ Inflammation contributes to early atherogenesis and progression of atherosclerotic lesions, and circulating inflammatory markers strongly correlate with ischemic events.²⁰ Furthermore, body composition and fat distribution may be important. Visceral adipose tissue (VAT) is a hyperinflammatory fat depot that is more metabolically harmful than subcutaneous

adipose tissue (SAT).²¹ VAT secretes a greater burden of proinflammatory cytokines than SAT, including interleukin-6, tumor necrosis factor- α , and monocyte chemotactic protein-1.²² These circulating inflammatory mediators may link adipose tissue inflammation to vascular inflammation, thereby increasing CV risk. Indeed, inflammation is a strong predictor of adverse CV outcomes in people with T1D.²³

SGLT-2 inhibitors and GLP-1 receptor agonists have cardiometabolic protective effects in people with and without T2D.²⁴ Adults and children with T1D have been excluded from CV outcome trials. Given the elevated CV risk in T1D, there is a compelling need to consider these medication classes. Efficacy and safety data from well-designed

Figure 1. Pathophysiological Contributors to Metabolic Dysfunction and CVD in T1D



Multiple pathophysiological contributors to metabolic dysfunction and CVD in T1D. Reprinted from Snaith JR et al. *Diabetes Care*, 2025; 49(1): 7-21. © by the American Diabetes Association.

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randomized controlled trials are needed to support their use in this patient population.

Practice Gaps

- A better understanding is needed of the mechanisms that specifically contribute to increased CV risk in T1D.
- Guidance is needed to identify patients with T1D who are at particularly high CV risk, in part due to insulin resistance, and who are most likely to benefit from cardioprotective metabolic adjunctive therapies.
- A better understanding is needed of the mechanisms of action and the risks and benefits of cardiometabolic adjunctive therapies for T1D.

Discussion

Only a few guidelines address the benefits and safe use of cardioprotective adjunctive agents in people with T1D. An in-depth understanding of the mechanisms of action, potential metabolic benefits, and risks associated with these medications is essential before they are offered off-label. In many cases, their use is driven by patients, based on data from mostly retrospective case note reviews of metabolic benefits. Few randomized, placebo-controlled trials have been published, and evidence from CV outcome trials is unavailable.

Metformin

Metformin improves insulin sensitivity and surrogate measures of vascular health (as measured by MRI-derived aortic pulse wave velocity) in youth with T1D.²⁵ In a 3-month randomized placebo-controlled trial of 48 adolescents with T1D, those randomly assigned to metformin, 2000 mg daily, exhibited more favorable changes in vascular health, insulin sensitivity, weight, and fat mass than placebo-treated individuals. Interestingly, insulin sensitivity also improved in normal-weight participants. Metformin had no

significant effect on hemoglobin A_{1c}, total daily insulin dose, blood pressure, or lipid profile.²⁵

In a recently published 26-week randomized, placebo-controlled trial of 40 adults with T1D,⁹ metformin had no effect on hemoglobin A_{1c}, liver or muscle insulin sensitivity (measured by clamp), adiposity, liver fat, or arterial stiffness. However, metformin reduced the insulin dose by 0.1 units/kg per day compared with placebo. The lack of change in insulin resistance suggests that metformin may have metabolic effects in T1D that are independent of changes in insulin action.

In the REMOVAL trial of 428 adults with T1D,²⁶ metformin had no effect on the progression of mean carotid artery intima media thickness (cIMT, the primary endpoint) over 3 years, although maximal cIMT (a prespecified tertiary outcome) was significantly reduced compared with placebo. Hemoglobin A_{1c} improved with metformin, driven by a temporary 0.24% reduction at 3 months ($P < .0001$). Metformin significantly reduced weight by 1.17 kg and LDL cholesterol by 0.13 mmol/L, and increased the estimated glomerular filtration rate by 4 mL/min per 1.73 m². The insulin dose was 0.023 units/kg per day lower in those assigned to metformin ($P = .0018$).

Taken together, these results suggest that metformin may have insulin-sensitizing and favorable metabolic effects in adolescents with T1D and, to a lesser extent, in adults, with the predominant effect appearing to be related to insulin dose reduction.

SGLT-2 Inhibitors

SGLT-2 inhibitors lower glucose by promoting renal tubular glucose excretion and have associated natriuretic effects. This medication class is approved for use in T2D to improve glycemic control, with trial data demonstrating significant benefits for CV, heart failure, and kidney outcomes.

Dapagliflozin was approved by the European Medicines Agency in 2019 for use in patients with T1D and overweight or obesity, and by the Japanese Ministry of Health, Labour, and Welfare

for the treatment of T1D in patients aged 15 years and older with insufficient glycemic control. However, the European Medicines Agency approval was retracted in 2021 due to concerns regarding the risk of (euglycemic) ketoacidosis. In a study using a propensity score-matched cohort of Japanese individuals with T1D, the incidence of ketoacidosis was slightly higher in patients prescribed dapagliflozin than in nonusers, but the confidence intervals were wide and overlapped.²⁷ The introduction of continuous ketone monitoring may reduce this risk in the future.

The Empagliflozin as Adjunct to inSulin therapy (EASE) trial program included 2 large double-blind, placebo-controlled phase 3 trials of empagliflozin in patients with T1D.²⁸ EASE-2 studied empagliflozin 10 mg (n = 243) and 25 mg (n = 244) vs placebo (n = 243) over 52 weeks. EASE-3 used empagliflozin 2.5 mg (n = 241), 10 mg (n = 248), and 25 mg (n = 245) vs placebo (n = 241) over 26 weeks. In both EASE-2 and EASE-3, all empagliflozin doses led to significant reductions in hemoglobin A_{1c} after 26 weeks. Placebo-adjusted hemoglobin A_{1c} reductions were highest with 10 mg (0.45% and 0.54%) and 25 mg (0.52% and 0.53%). Empagliflozin 2.5 mg significantly reduced hemoglobin A_{1c} by 0.28%. The beneficial effect on hemoglobin A_{1c} persisted at week 52 in EASE-2. Empagliflozin led to placebo-corrected reductions in body weight (up to 3.4 kg), total daily insulin dose (up to 13.3%), time-in-target range (up to 3.1 hours per day), and systolic blood pressure (up to 3.9 mm Hg), with similar results for the 10 mg and 25 mg doses between studies at 26 weeks. In EASE-3, empagliflozin 2.5 mg led to significant reductions in weight (1.8 kg), insulin dose (6.4%), and systolic blood pressure (2.1 mm Hg). One of the most noteworthy findings was that there were no excess cases of diabetic ketoacidosis with the 2.5 mg dose (0.8%) compared with placebo (1.2%), whereas the 10 mg (4.3%) and 25 mg (3.3%) doses showed higher rates. Whether empagliflozin 5 mg is associated with a heightened ketoacidosis risk is not known.

SGLT-2 inhibitors increase urinary glucose excretion and reduce insulin requirements, which can promote lipolysis and ketone production even when blood glucose levels are normal or only mildly elevated. In people with T1D, this increases the risk of euglycemic diabetic ketoacidosis, which may be harder to recognize because hyperglycemia is less prominent. To minimize this risk in patients with T1D treated with SGLT-2 inhibitors and insulin, the STICH protocol recommends stopping the SGLT-2 inhibitor, injecting an insulin bolus, consuming 30 g of carbohydrate, and hydrating if ketosis is detected.²⁹

GLP-1 Receptor Agonists

There are several misconceptions regarding the pathophysiology of T1D. The first concerns the assumption that people with T1D cannot secrete glucagon. Rather, despite a blunted glucagon response to hypoglycemia, people with T1D exhibit paradoxical, exaggerated postprandial glucagon secretion, which contributes to postprandial hyperglycemia. In addition, aberrant glucagon secretion contributes to glycemic variability in T1D.³⁰ Because exogenous insulin does not reach the paracrine levels of insulin secreted from β cells, it is ineffective in lowering postprandial glucagon levels.³¹

The second misconception is that most people with T1D cannot secrete insulin. Residual insulin secretion is, in fact, present in many individuals with T1D.³² It is best detected using high-sensitivity C-peptide assays (eg, ultrasensitive ELISA) after a meal, rather than during fasting. Fasting C-peptide is detectable in more than one-third of those with longstanding T1D, especially with postpubertal onset, and stimulated C-peptide (90 minutes after a mixed-meal tolerance test) is detectable in most (insulin microsecretors).³²

GLP-1 and GIP are incretin hormones critical to nutrient metabolism. Secreted by intestinal enteroendocrine cells, they activate receptors across broad sites, including pancreatic tissues (to promote insulin secretion and suppress postprandial glucagon secretion), the CV system,

and the central nervous system. Residual insulin secretion may be a target (and necessary) for GLP-1 receptor agonist action, although this remains unproven for the later-generation, longer-acting agents. Furthermore, glucagon suppression by GLP-1 receptor agonists may underlie potential therapeutic advantages over insulin monotherapy.

Recent studies have reported that people with T1D have a number of unmet needs, including simple and predictable diabetes management, reduced mental effort to manage diabetes, prevention of weight gain, achievement of a greater time-in-range, and prevention of hypoglycemia.^{33,34} Most participants surveyed would consider adding an adjunctive agent to insulin to address these unmet needs. The nutrient-stimulated hormone (NuSH) therapies, such as GLP-1 receptor agonists, help address these unmet needs in T1D.

In a retrospective study of a small number of people with newly diagnosed T1D, early initiation of semaglutide enabled most participants to discontinue insulin by 12 months. Semaglutide increased C-peptide levels and improved glycemic control.³⁵ Other retrospective real-world case-review studies have also suggested that semaglutide may benefit people with T1D. This hypothesis was tested in the ADJUST-T1D trial, which recruited 72 adults with obesity and T1D who used an automated insulin delivery system.³⁶ Participants were randomly assigned to receive once-weekly semaglutide (1 mg) or placebo for 26 weeks. The primary outcome was a composite endpoint of greater than 70% time-in-range, less than 4% time-in-hypoglycemia, and at least 5% weight reduction. This endpoint was achieved by 36% of patients in the semaglutide group and by none in the placebo group. Between-group differences in hemoglobin A_{1c}, weight, and total daily insulin dose were -0.3%, -8.8 kg, and -22.3 units, respectively. There were no safety concerns related to hypoglycemia or ketoacidosis. Several other randomized trials of semaglutide in T1D are recruiting.³⁷

GLP-1/GIP Receptor Agonists

Although GLP-1 and GIP share metabolic roles, they differ in their expression of adipose tissue receptors and in their effects on glucagon secretion. Specifically: (1) GIP receptors, but not GLP-1 receptors, are expressed in adipose tissue; and (2) whereas GLP-1 suppresses glucagon, GIP may promote its release in a glucose-dependent manner.^{38,39} When combined, GIP receptor activation synergistically boosts the therapeutic efficacy of GLP-1.^{40,41} Accordingly, dual GIP/GLP-1 receptor agonists, such as tirzepatide, have been developed to treat T2D and obesity.

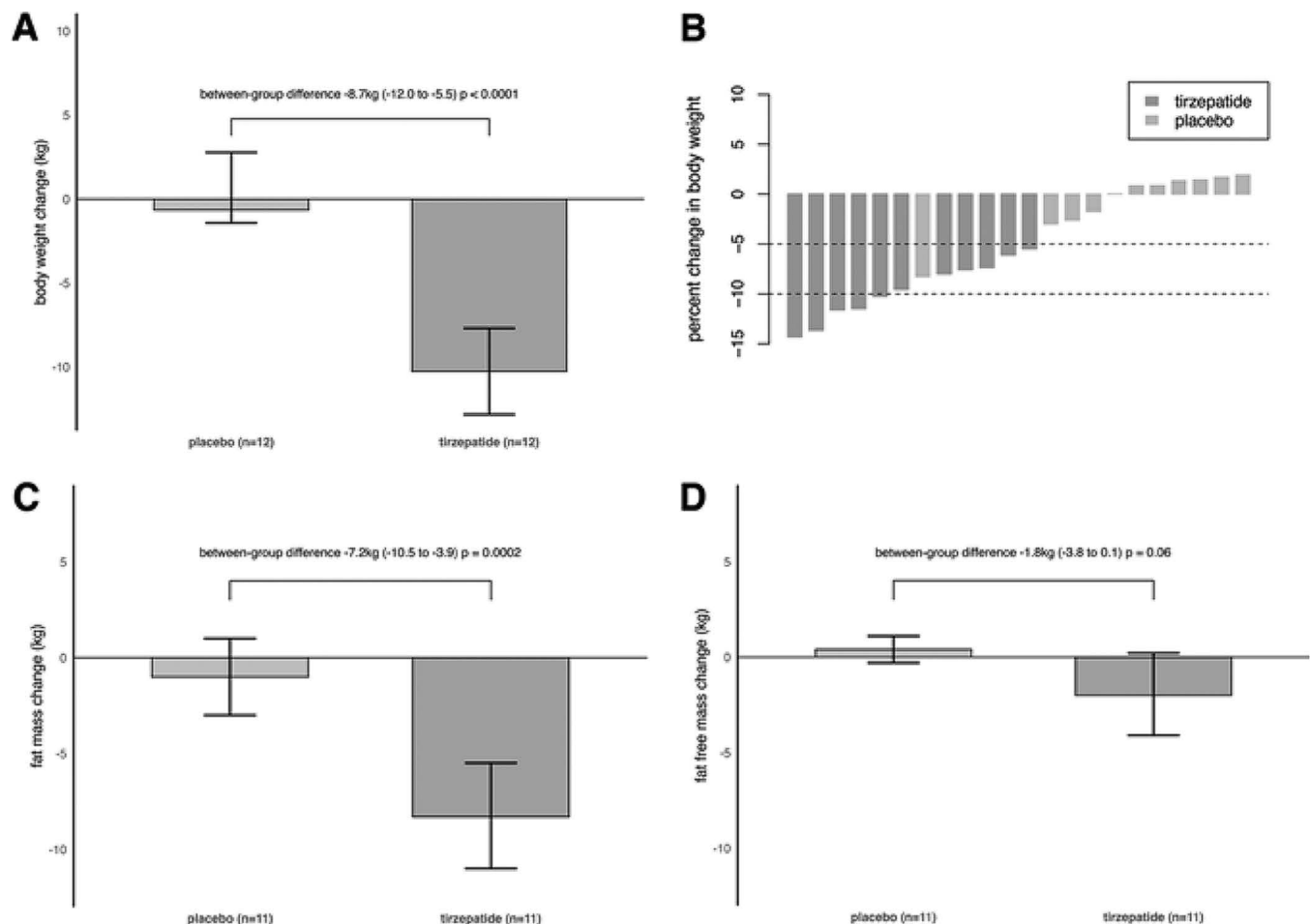
Tirzepatide is a first-in-class peptide that coagonizes GIP and GLP-1 receptors and is administered as a once-weekly subcutaneous injection. In the SURPASS program among people with T2D,⁴² tirzepatide demonstrated superiority over placebo in reducing hemoglobin A_{1c} and body weight at doses of 5 mg, 10 mg, and 15 mg over 40 weeks, without increasing hypoglycemia.⁴³ Separate obesity-focused trials (eg, SURMOUNT)⁴⁴ demonstrated tirzepatide's capacity to induce dose-dependent weight loss in people with obesity but without diabetes. These data established tirzepatide as highly effective at lowering glucose in people with T2D and reducing body weight in trial populations with overweight/obesity, with or without T2D, when titrated to a moderate-to-high target dose.⁴⁵

Tirzepatide has demonstrated clinically meaningful CV benefits beyond its glucose-lowering effect.⁴⁶ Recent CV outcome data establish that tirzepatide is at least noninferior to established GLP-1 receptor agonists (dulaglutide) for major adverse CV events and may offer additional reductions in all-cause mortality.⁴⁷ Emerging mechanistic evidence suggests that tirzepatide may exert direct cardioprotective effects by attenuating inflammatory,⁴⁸ profibrotic, hypertrophic, and apoptotic pathways in the diabetic myocardium, possibly mediated by improved insulin sensitivity.⁴⁹ Collectively, these findings highlight that tirzepatide has multifaceted CV benefits, with potential applicability in T1D.

TIRTLE1 is the first placebo-controlled, randomized study assessing tirzepatide (titrated to 5.0 mg over 12 weeks) in 24 individuals with T1D (mean age, 40.5 ± 11 years; BMI, 34.2 ± 3.4 kg/m²; hemoglobin A_{1c}, $7.3 \pm 1.3\%$; total daily insulin dose, 74.1 ± 26.8 units; 58% male; 50% using continuous subcutaneous insulin infusion).⁵⁰ The primary endpoint was change in body weight. At 12 weeks, tirzepatide had reduced body weight (mean difference -8.7 kg vs placebo, $P < .0001$), hemoglobin A_{1c} (mean difference -0.4% vs placebo, $P = .05$), and insulin dose (mean difference -35% vs placebo, $P = .0002$) (Figure 2). The reduction in

insulin dose was evident as early as 2 weeks after randomization among individuals using insulin pumps. Weight loss was predominantly fat mass (estimated treatment difference -7.2 kg [95% CI, -10.5 to -3.9 kg]; $P = .0002$); the between-group difference in lean mass was not significant. There were no episodes of diabetic ketoacidosis or severe hypoglycemia, and treatment satisfaction was favorable. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of tirzepatide in adults with overweight/obesity and T1D (SURPASS-T1D-1) is underway.

Figure 2. Effect of Once-Weekly Tirzepatide on Body Weight and Composition in Adults With T1D



Effect of once-weekly tirzepatide compared with placebo on body weight (primary outcome) and body composition in adults with type 1 diabetes. Panel A, The change from baseline in body weight at 12 weeks as assessed by ANCOVA, adjusted for baseline, with multiple imputation for missing data at 12 weeks. Panel B, Participant-level percentage change in body weight ordered on the x-axis from greatest decrease to increase, plotted by treatment group. All participants randomly assigned to tirzepatide experienced a $\geq 5\%$ decrease in body weight, and 45% experienced $\geq 10\%$ over the 12-week treatment period, compared with 9% and 0% in the placebo group. Panel C, Change in fat mass. Panel D, Change in fat-free mass. Error bars represent the 95% CI. Reprinted from Snaith JR et al. *Diabetes Care*, 2025; 49(1): 161-170. © by the American Diabetes Association.

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Clinical Case Vignettes

Case 1

A 42-year-old man with a 25-year history of T1D presents for follow-up. His medical history is notable for celiac disease, which was diagnosed 1 year before T1D. He uses a hybrid closed-loop insulin pump and a continuous glucose monitor. His total daily insulin dose (insulin aspart) is 97.2 units (59% basal insulin). His hemoglobin A_{1c} value is 7.1% (54 mmol/mol). Over the preceding 2 weeks, 60% of his glucose values were in the target range of 70 to 180 mg/dL (3.9-10 mmol/L), with no significant hypoglycemia. He has never had to use glucagon. His glucose coefficient of variation is 31.4%.

On physical examination, his weight is 195 lb (88.5 kg) (BMI = 30.6 kg/m²).

He would like to discuss the benefits and risks of oral diabetes adjunctive agents. He is particularly interested in using metformin and empagliflozin to reduce his total daily insulin dose and weight, with the ultimate aim of improving his CV risk profile.

Which of the following statements is correct?

- Metformin has been consistently shown to improve insulin sensitivity in youth with T1D but not in adults with T1D
- SGLT-2 inhibitors have been shown to be CV-protective in T1D trials
- SGLT-2 inhibitors are approved by the FDA and the European Medicines Agency for use in patients with T1D and overweight or obesity, but not in lean patients with T1D
- The lowest dosage of empagliflozin that effectively reduces hemoglobin A_{1c}, weight, and total daily insulin dose in T1D is 5 mg daily
- In T1D, the risk of diabetic ketoacidosis is increased with empagliflozin irrespective of dosage

Answer: A) Metformin has been consistently shown to improve insulin sensitivity in youth with T1D but not in adults with T1D

Unlike in people with T2D and in people without diabetes, there are no published data demonstrating that SGLT-2 inhibitors reduce CV events in T1D. Although SGLT-2 inhibitors were approved by the European Medicines Agency in 2019 for use in patients with T1D and overweight or obesity, the approval was revoked in 2021 due to concerns about the risk of ketoacidosis. The lowest effective dosage of empagliflozin for reducing hemoglobin A_{1c}, weight, and total daily insulin dose in T1D is 2.5 mg daily, and it carries a risk of ketoacidosis equivalent to that of placebo.

Case 1, Continued

If an SGLT-2 inhibitor were considered for this patient, which of the following would be the most important strategy to reduce the risk of diabetic ketoacidosis?

- Reducing basal insulin dosage to minimize hypoglycemia risk
- Ensuring routine home blood ketone monitoring with clear sick-day rules
- If empagliflozin is used, prescribing a dosage of only 5 mg daily
- Restricting carbohydrate intake to reduce postprandial hyperglycemia
- Targeting a lower glucose range in the hybrid closed-loop system

Answer: B) Ensuring routine home blood ketone monitoring with clear sick-day rules

Among the options listed, routine blood ketone monitoring with clear sick-day rules (Answer B) is the most important preventive strategy.

This includes patient education to:

- Measure blood ketones during illness, fasting, unexplained nausea, or persistent hyperglycemia
- Never stop background insulin, even if oral intake is reduced

- Temporarily discontinue the SGLT-2 inhibitor during intercurrent illness, surgery, or prolonged fasting
- Seek urgent medical attention if ketones remain elevated despite corrective actions

The other listed options are less effective or potentially harmful. Reducing basal insulin (Answer A) would increase the risk of insulin deficiency and ketoacidosis. The empagliflozin dose of 2.5 mg daily (Answer C) may reduce the risk of diabetic ketoacidosis. Restricting carbohydrates (Answer D) may exacerbate ketosis. Lowering glucose targets (Answer E) can increase variability in insulin delivery without addressing the underlying mechanism of diabetic ketoacidosis risk.

Therefore, structured education with proactive ketone monitoring and clear action plans is the cornerstone of ketoacidosis prevention when SGLT-2 inhibitors are used in patients with T1D.

Case 2

A 51-year-old man with a 32-year history of T1D consults you for the first time. His treatment includes insulin lispro, 10 units with meals, and insulin glargine, 15 units twice daily. He has taken rosuvastatin, 10 mg daily, and aspirin, 100 mg daily, for the past 5 years. He was hospitalized for diabetic ketoacidosis 11 years ago. His diabetes is complicated by proliferative retinopathy that was treated with laser therapy 15 years ago. His retinopathy is inactive. His history includes Addison's disease, coronary artery disease (stent inserted), hypertension, and dyslipidemia. His hemoglobin A_{1c} value is 9.8% (84 mmol/mol), and weight is 275 lb (125 kg) (BMI 40.8 kg/m²). His insulin dose is 0.48 units/kg per day. He is keen to trial adjunctive semaglutide.

Which of the following statements is correct?

- Fasting C-peptide should be measured to determine whether the patient will respond to semaglutide; if undetectable, he is unlikely to achieve a glycemic benefit or significant weight loss
- As glucagon secretion is nearly absent in T1D, semaglutide is unlikely to improve glycemic control
- Semaglutide has not been shown to reduce CVD in a CV outcomes trial in T1D
- Semaglutide is contraindicated due to the history of previously treated retinopathy
- A gastric emptying study should be performed before initiating semaglutide

Answer: C) Semaglutide has not been shown to reduce CVD in a CV outcomes trial in T1D

Semaglutide is only approved for T2D and obesity. While studies in patients with T2D have shown CV benefits, no dedicated, long-term CV outcomes trials have been conducted in a T1D population to prove these benefits, and the drug is not approved for T1D use. Current T1D data come from smaller randomized studies or retrospective analyses of off-label use, which are insufficient to establish a proven CVD risk-reduction indication in T1D.

Measuring stimulated, rather than fasting, C-peptide is more informative in patients with T1D. However, unlike with liraglutide, there is no evidence that the presence of C-peptide predicts response to semaglutide. Postprandial hyperglucagonemia contributes to hyperglycemia in T1D, and semaglutide suppresses hyperglucagonemia. Although there is evidence that rapid improvement in glycemic control, if achieved with insulin (particularly in pregnancy) or semaglutide, can hasten the progression of active retinopathy in people with T2D, this observation has not been tested in T1D. Although gastroparesis is a relative contraindication to using NuSH therapies in T1D, these therapies may still be effective in people with slow gastric emptying.

Case 2, Continued

The patient returns regularly for follow-up. He has been taking semaglutide, 1.0 mg weekly. After 2 years, his hemoglobin A_{1c} is 7.2% (55 mmol/mol), and weight is 255.1 lb (115.7 kg). His treatment includes insulin lispro, 1 unit per 7 g of carbohydrate 3 times daily, and insulin glargine, 12 units twice daily (total daily insulin dose = 42 units [0.36 units/kg per day]). He has had no hypoglycemia or ketoacidosis. He would like to switch from semaglutide to tirzepatide due to persistent nausea.

Which of the following statements is true?

- A. He is unlikely to achieve further weight loss or glycemic benefit from tirzepatide
- B. There is no randomized, placebo-controlled trial evidence demonstrating metabolic benefit of tirzepatide in T1D
- C. Tirzepatide should not be used in patients with T1D treated with hybrid closed-loop systems due to the risk of hypoglycemia
- D. Tirzepatide has been shown to slow gastric emptying less than semaglutide; hence, tirzepatide may be better tolerated than semaglutide
- E. Due to suppression of GLP-1–induced nausea by GIP, tirzepatide may be better tolerated than semaglutide

Answer: E) Due to suppression of GLP-1–induced nausea by GIP, tirzepatide may be better tolerated than semaglutide

Evidence suggests that the GIP component of tirzepatide may reduce the nausea often associated with GLP-1 receptor agonists, such as semaglutide. This mechanism has led to the hypothesis that tirzepatide may be better tolerated, particularly in terms of gastrointestinal adverse effects, than drugs like semaglutide, which primarily act as GLP-1 receptor agonists.

Tirzepatide may be a more potent NuSH than semaglutide in T1D because of GIP receptors in adipose tissue. Tirzepatide has shown significant weight loss and improved glycemic control

in people with T2D, and emerging evidence suggests potential benefits in T1D, particularly among those with higher BMI. The TIRTLE1 study demonstrated significant reductions in weight, hemoglobin A_{1c}, and total daily insulin dose in participants with T1D treated with tirzepatide. Although tirzepatide, like other GLP-1/GIP receptor agonists, may reduce insulin requirements and potentially increase the risk of hypoglycemia in some patients, there is no specific recommendation to restrict its use in those using hybrid closed-loop systems. In fact, hybrid closed-loop insulin systems might help mitigate the risk of hypoglycemia by adjusting insulin delivery in response to glucose changes. However, careful monitoring and dose adjustments are necessary, especially in patients using insulin pumps. Tirzepatide slows gastric emptying to a similar extent as semaglutide, which is one of the mechanisms contributing to nausea and other gastrointestinal adverse effects. Although there may be individual variability in tolerability, there is no solid evidence that slower gastric emptying makes tirzepatide significantly better tolerated than semaglutide.

Key Learning Points

- CV risk is significantly increased in T1D, driven by insulin resistance and inflammation, as well as by conventional vascular risk factors.
- Emerging evidence suggests that cardioprotective agents used to treat T2D, such as SGLT-2 inhibitors and GLP-1 receptor agonists, confer metabolic benefits in people with T1D. These medications are not approved for T1D at this time.
- Metformin's predominant effect in adults with T1D is to reduce the insulin dosage. Metformin is approved for T2D, but not for T1D (except in France).
- While empagliflozin reduces hemoglobin A_{1c}, weight, and total daily insulin requirements at dosages of 2.5 mg, 10 mg, and 25 mg, only the

2.5 mg dose is not associated with an increased risk of diabetic ketoacidosis.

- Patients who choose to use an SGLT-2 inhibitor off-label must be provided with specific instructions to reduce the risk of euglycemic ketoacidosis.

- Recent randomized, placebo-controlled trials demonstrate that both semaglutide and tirzepatide reduce weight, hemoglobin A_{1c}, and total daily insulin dose without increasing the risk of hypoglycemia or diabetic ketoacidosis.

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Managing Hyperglycemia in Hospitalized Patients

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the epidemiology, clinical significance, and adverse outcomes of hyperglycemia and hypoglycemia in hospitalized patients.
- Select appropriate inpatient pharmacologic therapies for hyperglycemia, emphasizing insulin-based regimens and the appropriate use or avoidance of noninsulin glucose-lowering medications, based on patient characteristics, clinical status, and current guideline recommendations.
- Navigate the inpatient use of continuous glucose monitoring systems by applying clinical guidelines, integrating institutional policies, and understanding safety requirements to ensure appropriate insulin dosing in hospitalized patients.

Significance of the Clinical Problem

Diabetes affects more than 38 million people in the United States, and it is the seventh leading cause of death.^{1,2} Individuals with diabetes are more likely to be hospitalized than those without diabetes, and this excess hospitalization imposes a substantial economic burden.^{3,4} Diabetes is among the most common conditions in hospitalized patients. According to the US Centers for Disease Control and Prevention, in 2020, there were approximately

8 million hospital discharges among adults in which diabetes was listed as a diagnosis. These discharges included ischemic heart disease, stroke, lower-extremity amputation, hyperglycemic crisis, and hypoglycemia.¹ Furthermore, nearly one-quarter of all adult hospitalizations in the United States include a diagnosis of diabetes, and the prevalence of hyperglycemia in the inpatient setting may approach 40% when stress-induced hyperglycemia is included.^{5,6} Hyperglycemia is associated with adverse clinical outcomes, including postoperative infections after cardiac and noncardiac surgery, acute kidney injury, myocardial infarction, and prolonged hospital stay.⁷⁻¹¹ Several studies have also demonstrated an association between inpatient hyperglycemia and increased mortality risk, particularly among individuals without preexisting diabetes who develop stress-induced hyperglycemia.^{6,12-15} Although it remains unclear whether this relationship is causal, the detrimental effects of severe hyperglycemia are well recognized and include volume depletion from osmotic diuresis and fluid shifts, electrolyte derangements, increased risk of infection, immune dysfunction, and impaired wound healing.¹⁶⁻¹⁸ Hypoglycemia during hospitalization is likewise associated with adverse clinical outcomes, including falls, prolonged length of stay, and increased in-hospital mortality.^{19,20} Hypoglycemia is the most common treatment-related complication of diabetes management, and patient-related risk factors for inpatient hypoglycemia include older age, longer duration of diabetes, impaired kidney or hepatic function, critical illness, inadequate nutritional intake, and a history of hypoglycemia.²⁰ In this context, maintaining euglycemia within a safe range during

hospitalization is critical for minimizing morbidity and reducing the risk of both hyperglycemic and hypoglycemic complications.

Diabetes care in the hospital differs markedly from outpatient management, and multiple factors unique to the inpatient environment complicate efforts to achieve optimal glycemic control. As a result, treating inpatient hyperglycemia remains challenging. In a recently published randomized controlled trial, a substantial proportion of hospitalized adults with type 2 diabetes in non-intensive care unit wards had continuous glucose monitoring (CGM) mean glucose levels greater than 180 mg/dL (>10.0 mmol/L)—33% in the intensive treatment group and 52% in the standard care group—despite treatment by specialized glycemic management teams at academic medical centers.²¹ In the inpatient setting, patients frequently experience acute physiological stress, with accompanying hormonal and inflammatory changes that promote hyperglycemia and insulin resistance.²² Physical activity is often limited, and nutritional intake can be highly unpredictable in amount and timing. Furthermore, enteral or parenteral nutrition, along with medications such as glucocorticoids and vasopressors, can contribute to significant hyperglycemia.²² Additional factors that complicate glycemic control include holding outpatient noninsulin medications, coordinating prandial insulin administration with meals, rapid changes in insulin requirements, and various transitions of care.

Practice Gaps

- Despite the high prevalence and clinical importance of inpatient hyperglycemia, effective management remains challenging in routine clinical practice, and a substantial proportion of hospitalized patients fail to achieve recommended glycemic targets.
- Familiarity with and understanding of guidelines for the use of various insulin regimens and noninsulin glucose-lowering agents in hospitalized patients may be limited,

leading to inconsistent practice patterns, preventable adverse events, and missed opportunities to optimize patient outcomes.

Discussion

The American Diabetes Association (ADA) defines hyperglycemia in hospitalized patients as random blood glucose levels above 140 mg/dL (>7.8 mmol/L).²³ Elevated blood glucose may be observed in patients with known diabetes, those with previously undiagnosed diabetes, and those experiencing stress-induced hyperglycemia. The ADA recommends measuring hemoglobin A_{1c} in all patients with diabetes or hyperglycemia admitted to the hospital if it has not been obtained in the previous 3 months.²³ Knowledge of preadmission glycemic status helps guide inpatient management and posthospital care planning. In individuals without a known history of diabetes, an admission hemoglobin A_{1c} value of 6.5% or greater (≥ 48 mmol/mol) suggests previously unrecognized diabetes rather than stress-induced hyperglycemia.²³ Guidelines on inpatient hyperglycemia management recommend point-of-care (POC) blood glucose monitoring before meals and at bedtime.²⁴ When a patient is nil per os (NPO), blood glucose should be checked every 4 to 6 hours. Testing should be performed using professional glucose meters cleared by the US FDA for hospital use.²³

When defining inpatient glycemic targets, guidelines from international societies consistently recommend an upper blood glucose limit of 180 mg/dL (10.0 mmol/L), although recommendations for the lower threshold vary.²⁴ Much of the evidence supporting these glycemic goals originates from studies in critically ill patients, with subsequent extrapolation to noncritical care settings.^{23,24} The ADA recommends a target blood glucose range of 100 to 180 mg/dL (5.6–10.0 mmol/L) for most noncritically ill patients.²³ For critically ill patients, a target range of 140 to 180 mg/dL (7.8–10.0 mmol/L) is recommended, while a lower target of 110 to 140 mg/dL (6.1–7.8 mmol/L) may be considered

in certain populations, such as patients undergoing cardiac surgery, provided it can be achieved without increasing the risk of hypoglycemia.²³ For patients treated with basal insulin, fasting glucose values less than 100 mg/dL (<5.6 mmol/L) are associated with an increased risk of hypoglycemia the following day. Accordingly, when blood glucose falls below this threshold, therapy should be reevaluated to reduce the risk of hypoglycemia.^{25,26} A higher target range, up to 250 mg/dL (13.9 mmol/L), may be justified for individuals with terminal illness, limited life expectancy, or a substantial risk of hypoglycemia.^{23,26} In patients receiving continuous enteral or parenteral nutrition, targeting a glucose level less than 140 mg/dL (<7.8 mmol/L) increases the risk of hypoglycemia and is not recommended.²³

Insulin remains the preferred therapy for managing hyperglycemia in most hospitalized patients, particularly those who are critically ill.^{23,24,26,27} In the intensive care unit, continuous intravenous insulin infusion is recommended.²³ Among noncritically ill patients, subcutaneous insulin regimens are commonly used, most often as scheduled basal-bolus therapy.^{23,24} Patients with type 1 diabetes require uninterrupted basal insulin to prevent severe hyperglycemia and diabetic ketoacidosis. To reduce the risk of inadvertent omission, particularly during transitions in care, electronic medical record systems should incorporate safety mechanisms, such as best-practice alerts, to ensure consistent administration of basal insulin, whether subcutaneously, via an insulin pump, or intravenously.^{23,26} In noncritically ill patients with type 2 diabetes, insulin is also typically the treatment of choice because it is effective, has no upper dosing limit, can be readily adjusted as clinical status evolves, and is not subject to the inpatient contraindications that limit many oral agents.²² However, carefully selected patients with type 2 diabetes—such as those who are well controlled on their outpatient regimen, clinically stable, eating regularly, and without current or anticipated inpatient contraindications—may be eligible to continue their home oral glucose-lowering medications during hospitalization.^{23,26}

In many instances, it is appropriate to resume noninsulin therapies in clinically stable patients before discharge, as part of a planned transition to outpatient care.²⁷ Growing evidence indicates that DPP-4 inhibitors can be a reasonable inpatient option for managing mild hyperglycemia among eligible patients with type 2 diabetes.²⁷ In addition, data support the use of SGLT-2 inhibitors in individuals with type 2 diabetes who are admitted for heart failure, once clinically stable and in the absence of contraindications.²³

Clinical Case Vignettes

Case 1

A 70-year-old man with a 4-year history of type 2 diabetes, hypertension, and stage 3a chronic kidney disease presents to the emergency department with recurrent nausea, vomiting, and diarrhea. Oral intake has been poor for the past 2 days. His diabetes is managed only with diet, and his most recent hemoglobin A_{1c} value 1 month ago was 6.5% (48 mmol/mol). On physical examination, his blood pressure is 110/62 mm Hg, and pulse rate 98 beats/min. His height is 63.4 in (161 cm), and weight is 143.3 lb (65 kg) (BMI = 25.1 kg/m²).

Laboratory test results:

Blood glucose = 145 mg/dL (SI: 8.1 mmol/L)
Creatinine = 3.2 mg/dL (SI: 282.9 μmol/L) (increased from a baseline 1.5 mg/dL [132.6 μmol/L])

The rest of the results from the complete metabolic panel are normal.

He is admitted to general medicine for ongoing care, and an initial inpatient diabetes management strategy is required.

Which of the following is the best initial treatment for this patient?

- Start insulin glargine, 20 units once daily
- Start rapid-acting or short-acting correctional insulin based on POC blood glucose readings before meals or every 6 hours if the patient is NPO

- C. Start insulin glargine, 20 units once daily, plus rapid-acting correctional insulin
- D. Start continuous intravenous insulin infusion with a glycemic goal of 140 to 180 mg/dL (7.8–10.0 mmol/L)
- E. Recommend no pharmacologic therapy or bedside blood glucose monitoring

Answer: B) Start rapid-acting or short-acting correctional insulin based on POC blood glucose readings before meals or every 6 hours if the patient is NPO

Most clinical practice guidelines recommend managing inpatient hyperglycemia with scheduled basal-bolus insulin therapy rather than relying solely on correctional insulin.²⁴ Nevertheless, in a subset of patients with stress-induced hyperglycemia or type 2 diabetes and mild hyperglycemia, correctional insulin therapy alone may be appropriate when blood glucose levels remain below 180 mg/dL (<10.0 mmol/L).²³ Consistent with this approach, the Endocrine Society guidelines for inpatient hyperglycemia management in noncritically ill adults suggest initial treatment with correctional insulin alone in patients with newly recognized hyperglycemia, and in selected patients with diabetes previously managed with diet or noninsulin medications, when admission blood glucose is less than 180 mg/dL (<10.0 mmol/L). Scheduled insulin therapy should be initiated in patients with persistent hyperglycemia—defined as 2 or more glucose readings of 180 mg/dL or higher (≥10.0 mmol/L) in a 24-hour period—despite correctional insulin.²⁷

When selecting the most appropriate inpatient diabetes treatment, the risk of hypoglycemia should be carefully considered. Hypoglycemia is defined as blood glucose less than 70 mg/dL (<3.9 mmol/L) and is subdivided into 3 categories:

- Level 1: blood glucose 54–69 mg/dL (3.0–3.8 mmol/L)
- Level 2: blood glucose <54 mg/dL (<3.0 mmol/L)
- Level 3: severe hypoglycemia marked by cognitive or physical impairment requiring external assistance²³

Multiple factors are associated with an increased risk of hypoglycemia, including age 65 years or older, BMI of 27 kg/m² or lower, chronic kidney disease (stage 3 or higher), advanced liver disease, congestive heart failure, cerebrovascular disease, malignancy, and a history of hypoglycemia before or during past hospitalizations.²⁷

This patient has well-controlled type 2 diabetes on diet alone and now presents with an acute illness associated with poor oral intake and acute kidney injury. His blood glucose at hospital admission is only mildly elevated, making him an appropriate candidate for correctional insulin therapy alone as initial treatment. Furthermore, his risk factors for hypoglycemia, including advanced age, relatively low BMI, and kidney disease, warrant a cautious approach. Initiating scheduled basal insulin with 20 units of insulin glargine (Answers A and C) would be overly aggressive. Initial dosing for scheduled insulin therapy can be guided by estimating the total daily dose (TDD), which is weight-based and adjusted for insulin sensitivity, with recommended starting doses of 0.2 to 0.6 units/kg per day.^{23,26} TDDs exceeding 0.6 units/kg per day have been linked to increased hypoglycemia risk.²⁸ In older adults (≥70 years) and in patients with chronic kidney disease (stage 3 or higher), lower initial doses (TDD 0.2–0.3 units/kg per day) are recommended.²⁶ Approximately 50% of the calculated TDD is administered as basal insulin, with the remainder given as nutritional insulin.^{23,26} In this patient, initiating insulin glargine at 20 units would result in a basal insulin dose greater than 0.3 units/kg per day, which is substantially higher than recommended. Continuous intravenous insulin infusion (Answer D) is reserved for critically ill patients or those with severe hyperglycemia. Ongoing glucose monitoring remains necessary during acute illness, even when pharmacologic therapy is minimal, so recommending no pharmacologic therapy or bedside blood glucose monitoring (Answer E) is incorrect.

Case 2

A 53-year-old man with type 2 diabetes is hospitalized for community-acquired pneumonia. He initially presented to the emergency department with cough, shortness of breath, fever, chills, malaise, and loss of appetite. He reported not eating for more than 24 hours. Due to concerns about his ability to maintain oral intake, he was admitted to the general medicine ward. His medical history includes class 1 obesity, hypertension, mixed dyslipidemia, and tobacco use. His diabetes is complicated by moderately increased albuminuria, and his outpatient diabetes regimen consists of empagliflozin, 25 mg daily. His most recent hemoglobin A_{1c}, measured 6 weeks ago, was 6.4% (46 mmol/mol). On admission to the hospital, his blood glucose was 168 mg/dL (9.3 mmol/L). Kidney function is normal, and there is no metabolic acidosis or ketosis. The primary team requests an endocrinology consultation for inpatient diabetes management.

Which of the following is the most appropriate inpatient diabetes management strategy?

- A. Continue empagliflozin, 25 mg daily, and start rapid-acting correctional insulin before meals or every 6 hours if NPO
- B. Continue empagliflozin, 25 mg daily, and monitor blood glucose; start long-acting insulin and correctional insulin if 2 or more glucose readings are ≥ 180 mg/dL (≥ 10.0 mmol/L) in a 24-hour period
- C. Continue empagliflozin, 25 mg daily, and add linagliptin, 5 mg daily, plus correctional insulin before meals or every 6 hours if NPO
- D. Hold empagliflozin during hospitalization; start semaglutide, 0.25 mg subcutaneous injection once weekly, and correctional insulin before meals or every 6 hours if NPO
- E. Hold empagliflozin during hospitalization; start sitagliptin, 100 mg once daily, and correctional insulin before meals or every 6 hours if NPO

Answer: E) Hold empagliflozin during hospitalization; start sitagliptin, 100 mg once daily, and correctional insulin before meals or every 6 hours if NPO

SGLT-2 inhibitors lower plasma glucose by inhibiting glucose reabsorption in the proximal renal tubule, thereby increasing urinary glucose excretion.²⁹ Currently available SGLT-2 inhibitors include canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin, all of which are US FDA-approved. Beyond glycemic control, this class of medications confers cardiovascular and renal benefits and is approved for the treatment of type 2 diabetes, heart failure, and chronic kidney disease.^{30,31} With the increasing use of these agents, clinicians can expect to encounter them more often in hospitalized patients.³²

SGLT-2 inhibitors also have potential adverse effects that warrant consideration. The most common are genital mycotic infections. Urinary tract infections have also been reported, along with rare cases of Fournier gangrene.^{30,33} In addition, these agents cause osmotic diuresis, which may increase the risk of volume depletion, particularly when used concomitantly with other diuretics.³³ Diabetic ketoacidosis (DKA) is an uncommon but serious adverse event that has been reported as a class effect with SGLT-2 inhibitors.^{33,34} The risk is particularly increased in patients with type 1 diabetes when SGLT-2 inhibitors are used off-label, but it can also occur in patients with type 2 diabetes.³⁴ DKA associated with SGLT-2 inhibitors often presents as euglycemic diabetic ketoacidosis (blood glucose < 200 mg/dL [< 11.1 mmol/L]), which can delay recognition because there is no significant hyperglycemia.^{33,34} Although the precise pathophysiology of SGLT-2 inhibitor-associated DKA is not fully understood, it likely reflects multiple mechanisms, including a reduced insulin-to-glucagon ratio, increased lipolysis and ketogenesis, and impaired renal excretion of ketone bodies.^{33,34} Precipitating factors for SGLT-2 inhibitor-associated DKA include prolonged fasting, poor oral intake, very low-carbohydrate or ketogenic diet, dehydration, volume depletion, vomiting, acute infection or

severe acute medical illness, hospitalization for surgery, insulin omission or inappropriate dose reduction, excessive alcohol intake, and vigorous or prolonged exercise.³⁴⁻³⁶

In this case, the patient is hospitalized with an acute infection and reports poor oral intake, both of which are recognized risk factors for euglycemic DKA; therefore, continuing empagliflozin would not be advisable (Answers A, B, and C). According to the most recent ADA Standards of Care, inpatient initiation or continuation of SGLT-2 inhibitor therapy is recommended for heart failure indications once the acute illness has resolved and there are no contraindications.²³ However, SGLT-2 inhibitors are not recommended for routine inpatient glycemic management and should be withheld in the presence of ketonemia or ketonuria, prolonged fasting, severe illness, or in the perioperative setting.²³ The FDA recommends discontinuing these agents 3 days before scheduled surgical procedures (4 days in the case of ertugliflozin).³⁰ SGLT-2 inhibitor therapy may be resumed postoperatively once normal nutritional intake has resumed.³⁰

GLP-1 receptor agonists are incretin-based therapies that stimulate glucose-dependent insulin secretion, suppress glucagon release, reduce appetite, and delay gastric emptying.³⁷ These agents have intermediate to very high glucose-lowering efficacy, promote clinically meaningful weight loss, and are associated with cardiovascular benefits.³⁷ In many cases, GLP-1 receptor agonists are recommended as initial therapy for type 2 diabetes and have substantially transformed medical weight management. Semaglutide, a GLP-1 receptor agonist, has also demonstrated benefits in diabetic kidney disease and is available as either a once-weekly subcutaneous injection or a once-daily oral formulation.³⁸ However, data on the use of GLP-1 receptor agonists in hospitalized patients remain limited.³⁹⁻⁴¹ Although these agents can improve glycemic control, gastrointestinal adverse effects are a significant barrier to inpatient use. The most common adverse effects include nausea, vomiting, constipation, diarrhea, and decreased appetite.³⁷ A systematic review found an approximately 6-fold higher risk of nausea or vomiting in hospitalized

patients treated with GLP-1 receptor agonists compared with insulin.⁴¹ In this context, the ADA recommends holding GLP-1 receptor agonists during acute illness in hospitalized patients.²³

In the clinical vignette, initiation of semaglutide (Answer D) would not be appropriate in the inpatient setting because of its prolonged titration period, delayed onset of glucose-lowering effect, and potential for poor gastrointestinal tolerance. However, given the patient's history of obesity, cardiovascular risk factors, and moderately increased albuminuria, semaglutide could be considered in the outpatient setting—potentially in combination with empagliflozin—due to its cardiometabolic and renal benefits, despite adequate glycemic control, as reflected by his hemoglobin A_{1c}.

DPP-4 inhibitors are oral agents that block the enzymatic activity of DPP-4, a protease that degrades incretin hormones, including GLP-1 and glucose-dependent insulinotropic polypeptide.⁴² By increasing circulating levels of these incretins, DPP-4 inhibitors augment glucose-dependent insulin secretion and suppress glucagon release, thereby reducing fasting and postprandial plasma glucose levels.⁴² These agents are associated with intermediate glucose-lowering efficacy, minimal risk of hypoglycemia, and good tolerability.⁴² Currently available DPP-4 inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin. Clinically relevant differences among agents in this class relate primarily to renal dosing requirements and heart failure risk. Renal dose adjustment is necessary for sitagliptin, saxagliptin, and alogliptin but not for linagliptin.²³ In addition, saxagliptin and alogliptin carry an FDA warning for a possible increased risk of heart failure, especially among patients with preexisting cardiac or kidney disease.⁴³

Evidence from a limited number of randomized trials suggests that DPP-4 inhibitors effectively control blood glucose in hospitalized patients with type 2 diabetes and mild-to-moderate hyperglycemia.^{44,45} DPP-4 inhibitors are associated with a lower incidence of hypoglycemia than insulin in hospitalized patients.⁴¹ The Endocrine Society guidelines for the management of

hyperglycemia in noncritically ill hospitalized adults suggest consideration of a DPP-4 inhibitor plus correctional insulin in selected patients with type 2 diabetes, regardless of previous outpatient DPP-4 inhibitor use, who have a recent hemoglobin A_{1c} value less than 7.5% (<58 mmol/mol) and admission blood glucose levels less than 180 mg/dL (<10.0 mmol/L).²⁷ For patients treated with insulin before hospitalization, a DPP-4 inhibitor-based regimen may be considered if the total daily insulin dose is less than 0.6 units/kg per day. These recommendations exclude patients with type 1 diabetes and other insulin-dependent forms of diabetes.²⁷ Escalation to scheduled insulin therapy is recommended if hyperglycemia persists, defined as blood glucose levels of 180 mg/dL or higher (≥ 10.0 mmol/L), despite treatment with a DPP-4 inhibitor and correctional insulin.²⁷ Consistent with this, the ADA notes that DPP-4 inhibitor therapy, with or without basal insulin, may represent a lower-risk, less-complex treatment approach for patients with admission blood glucose levels less than 180 to 200 mg/dL (10.0–11.1 mmol/L).²³ In the presented case, the patient's hemoglobin A_{1c} was 6.4% (46 mmol/mol) before admission while receiving a single oral glucose-lowering agent, and his admission blood glucose was 168 mg/dL (9.3 mmol/L), making him an appropriate candidate for treatment with sitagliptin plus correctional insulin (Answer E).

Case 3

A 32-year-old woman with type 1 diabetes presents to the emergency department with chest pain. She was diagnosed with diabetes at age 10 and is treated with a multiple daily injection insulin regimen. Her most recent hemoglobin A_{1c} value, measured 2 months before admission, was 6.5% (48 mmol/mol). She uses a personal CGM. On admission, her blood glucose is 138 mg/dL (7.7 mmol/L), with no evidence of metabolic acidosis or ketosis. She is alert and oriented and demonstrates an appropriate understanding of her medical condition. The initial evaluation for chest pain is unrevealing, and she is admitted to

the general medicine service for observation and further workup. The primary team consults you for assistance with inpatient diabetes management. Shortly after admission, the bedside nurse contacts you to report that the patient is refusing POC blood glucose monitoring with the hospital glucometer and requests that nursing staff rely solely on her personal CGM readings.

Which of the following is the most appropriate response?

- Explain to the patient that POC blood glucose monitoring is required by hospital policy and that continued refusal may result in discharge from the hospital
- Instruct the nursing staff to use the patient's CGM readings in place of POC blood glucose measurements for insulin dosing decisions
- Explain to the patient that personal CGM devices are not FDA-approved for inpatient use and that, although continued use of her CGM may be permitted, confirmatory POC blood glucose measurements are required for insulin dosing decisions under the current hospital protocol
- Explain to the patient that the ADA standards of care recommend against the use of personal CGM devices during hospitalization
- Ask the nurse to request an urgent evaluation by the primary team for altered mental status, as refusal of POC glucose monitoring suggests delirium

Answer: C) Explain to the patient that personal CGM devices are not FDA-approved for inpatient use and that, although continued use of her CGM may be permitted, confirmatory POC blood glucose measurements are required for insulin dosing decisions under the current hospital protocol

Interest in using CGM devices in hospitalized patients with diabetes has grown. During the COVID-19 pandemic, the FDA permitted outpatient CGM systems in the inpatient setting under temporary enforcement discretion to enable remote glucose monitoring, reduce health

care worker exposure, and conserve personal protective equipment.⁴⁶ As a result, multiple hospitals in the United States implemented institutional protocols and generated clinical experience with inpatient CGM use. Emerging evidence, including data from randomized controlled trials, suggests that adding CGM to standard care improves glycemic control and reduces the frequency of hypoglycemia—including severe and nocturnal hypoglycemia—compared with POC glucose testing alone.⁴⁷ The Endocrine Society recommends real-time CGM with confirmatory POC blood glucose measurements in selected noncritically ill hospitalized adults at increased risk for hypoglycemia, when appropriate institutional resources and trained personnel are available.²⁷ Clinicians should be aware of potential limitations of CGM use in the inpatient setting, including medication interference that may affect the accuracy of specific devices (eg, high-dose acetaminophen [>1 g every 6 hours], ascorbic acid [>500 mg daily], or hydroxyurea), physiologic lag between interstitial and blood glucose during rapid glycemic changes, and clinical conditions such as tissue hypoperfusion or altered volume status.^{27,46} The ADA standards of care support the continued use of personal CGM devices during hospitalization when clinically appropriate and when implemented in institutions with established protocols, while recommending confirmatory POC glucose measurements to guide insulin therapy.²³

In this case, Answer C is the most appropriate response because personal CGM devices are not currently FDA-approved for inpatient insulin dosing, and guidelines recommend confirmatory POC blood glucose measurements for insulin management under most hospital protocols. Answer A is inappropriate because threatening discharge is not patient-centered and is unnecessarily punitive. Answer B is incorrect because relying solely on personal CGM data for insulin dosing without validation is not supported by current guidelines. Answer D is incorrect because the ADA does not recommend against CGM use in hospitalized patients; rather, it supports continued use with safeguards. Answer E

is inappropriate because the patient demonstrates intact cognition and understanding, with no evidence of delirium.

In some centers, institutional policies permit the use of personal CGM devices instead of routine POC blood glucose monitoring, provided a CGM validation process supports insulin management decisions.⁴⁸ Published validation criteria exist to assess CGM accuracy in the inpatient setting. One commonly used standard is the 20/20 criterion, which requires CGM values to be within $\pm 20\%$ of the corresponding POC blood glucose measurement (or within ± 20 mg/dL [1.1 mmol/L] when blood glucose is <70 mg/dL [<3.9 mmol/L]).^{23,48} In the absence of FDA approval for inpatient use, CGM-guided insulin dosing remains institution-dependent, and off-label inpatient use requires acknowledgment of device limitations and explicit patient agreement.⁴⁸

Key Learning Points

- Inpatient hyperglycemia is common, clinically significant, and often challenging to manage. Effective treatment requires evidence-based strategies and an individualized approach that balances the risks of hyperglycemia and hypoglycemia during acute illness.
- Insulin remains the cornerstone of inpatient hyperglycemia management, while selected noninsulin glucose-lowering agents may be used in carefully chosen patients based on clinical stability, nutritional status, and guideline recommendations.
- Continuous glucose monitoring can be used in hospitalized patients when supported by institutional protocols and either confirmatory POC blood glucose testing for insulin dosing or CGM validation standards to ensure safe use.

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GLP-1 Receptor Agonists and Pancreatitis and Pancreatic Lesions: What Is the Evidence and When Are They Contraindicated?

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Stop measuring pancreatic enzymes as a precaution for people receiving GLP-1 receptor agonists (GLP-1 RAs).
- Use GLP-1 RAs in people with a history of pancreatitis from other causes.
- Use GLP-1 RAs in people with pancreatic lesions, with an understanding of the uncertainty regarding the effect of these medications on the risk of pancreatic cancer in individuals at high risk.

Significance of the Clinical Problem

GLP-1 RA and GLP-1/GIP dual agonist (GLP-1/GIP DA) medications are effective for glycemic control and for preventing weight- and diabetes-related complications. GLP-1 RAs account for about 35% of prescriptions for type 2 diabetes (T2D) and obesity, and about 7% of prescriptions for obesity.¹ For the first time, the obesity rate in the United States is expected to decline.²

Use of GLP-1 RA or GLP-1/GIP DA therapy reduces the risk of comorbidities, and long-term use of these agents is expected to prevent about 8000 to 10,000 cases of cardiovascular disease (CVD) per 100,000 individuals treated, with an incremental quality-adjusted life-year gain of 0.25 to 0.35.³ However, some time ago, use of GLP-1 RAs was reported to be associated with increased risks of acute pancreatitis⁴ and adenocarcinoma of the pancreas.⁵ The FDA has never recommended against using GLP-1 RA and GLP-1/GIP DA in people at higher risk of pancreatic cancer or acute pancreatitis. However, clinical practice guidelines advise that in individuals with a history of pancreatitis, use of incretin medications (ie, GLP-1 RA, GLP-1/GIP DA, and DPP-4 inhibitor) should be avoided.⁶ Inappropriate withholding of these agents from patients with clear indications for their use deprives them of their benefits.

Practice Gaps

- Due to earlier reports suggesting a potential association between GLP-1 RAs and pancreatitis or pancreatic cancer, as well as concerns expressed by some experts, clinicians often avoid prescribing these agents

to individuals considered at risk for these conditions.

- Some clinicians periodically monitor pancreatic enzyme levels in patients receiving a GLP-1 RA or GLP-1/GIP DA.
- It is unclear whether these precautions deprive patients of the benefits of these agents or are reasonable measures to prevent harm.

Discussion

There is robust evidence supporting the efficacy of GLP-1 RA and GLP-1/GIP DA in glycemic control, weight loss, cardiovascular (CV) and kidney protection, and emerging roles in other metabolic and obesity-related conditions. Specific indications⁷ for 1 or more of these agents include:

- To improve glycemic control as an adjunct to diet and exercise in adults with T2D.
- To reduce excess body weight and maintain long-term weight loss in combination with a reduced-calorie diet and increased physical activity in adults with obesity, and in adults with overweight in the presence of at least 1 weight-related comorbid condition.
- To reduce the risk of major adverse cardiovascular events (MACE) in adults with established CVD and T2D, obesity, or overweight, and in people at high risk of these events and T2D.
- To reduce the risk of sustained estimated glomerular filtration rate decline, end-stage kidney disease, and CV death in adults with T2D and chronic kidney disease (CKD).
- To treat noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) in adults with moderate-to-advanced liver fibrosis (stages F2 to F3).
- To treat moderate-to-severe obstructive sleep apnea (OSA) in adults with obesity.

The perceived risk of adverse effects (eg, pancreatitis and pancreatic cancer) limits the use of GLP-1 RA and GLP-1/GIP DA medications in

real-world settings⁸ These conditions occur more often in people with excess weight and diabetes, the population in which these drugs are most commonly used.

Pancreatic Masses

A pancreatic mass is identified in about 50% of autopsies and in 15% to 75% of cross-sectional imaging studies, more often in elderly individuals.⁹ About one-half to three-fourths of patients with high-risk stigmata and one-quarter of those with worrisome features already have malignancy.¹⁰ Risk of pancreatic cancer goes up with increasing body weight (by 10% for every 5-point increase in BMI) and the presence of diabetes (by 50% [95% CI, 40%-60%]).¹¹

Pancreatic Cancer

Although earlier studies suggested a relationship between incretin-based therapy and pancreatic cancer,⁵ several recent robust studies have not confirmed this. A recent meta-analysis of randomized, placebo-controlled trials¹² included 48 trials with 94,245 participants. It demonstrated, with moderate certainty, that GLP-1 RAs probably have little or no effect on pancreatic cancer risk (odds ratio, 0.84 [95% CI, 0.53-1.35]). Observational studies suggest that GLP-1 RAs, compared with other antidiabetes drugs, may be associated with a lower risk of obesity-related cancers, including pancreatic cancer (vs insulin: hazard ratio, 0.41 [95% CI, 0.33-0.50]).¹³

Most often, pancreatic adenocarcinomas arise from precancerous lesions, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. Between 8% and 25% of people with IPMNs develop pancreatic adenocarcinoma over a 10-year period.¹¹ This risk is higher when more family members have a history of pancreatic cancer, with a standardized incidence ratio of 4.9 (95% CI, 4.0-5.9). This is more likely when there are more family members with a history of pancreatic cancer, especially if it occurs at a younger age.¹¹ Therefore, some health care providers are cautious about using GLP-1 RAs in people at higher risk of pancreatic

adenocarcinoma. However, no studies have specifically investigated whether GLP-1 RAs modify risk in people at higher-than-normal risk of pancreatic cancer.

Acute Pancreatitis

Risk factors for acute pancreatitis include hypertriglyceridemia, gallstone disease, excessive alcohol use, and smoking.¹⁴ Earlier studies suggested a relationship between incretin-based therapy use and acute pancreatitis.⁴ The 2 major indications for these therapies are diabetes and obesity, which by themselves pose a risk for acute pancreatitis; diabetes increases the risk by 75% (95% CI, 33%-129%)¹⁵ and obesity increases the risk by 180% (95% CI: 80%-330%).¹⁶ Moreover, hypertriglyceridemia, which dose-dependently relates to the rates of local complications of pancreatitis, organ failure, and maximum C-reactive protein level, is significantly and dose-dependently related to obesity and uncontrolled diabetes.¹⁷

Recent robust studies based on randomized controlled trials demonstrate no association between GLP-1 RA use and acute pancreatitis. A recent meta-analysis¹⁸ included 55 placebo-controlled trials involving 106,395 participants and found that GLP-1 RA use has little or no effect on pancreatitis risk (relative risk, 0.96 [95% CI, 0.67-1.38]). Other meta-analyses of randomized controlled trials¹⁹ have also shown no association between GLP-1 RA use and episodes of acute pancreatitis.

Diagnosis of Acute Pancreatitis

Diagnosis of acute pancreatitis is established by the presence of 2 of the 3 following:

- (i) abdominal pain consistent with the disease
- (ii) serum amylase and/or lipase greater than 3 times the upper limit of normal, and/or
- (iii) characteristic findings on abdominal imaging²⁰

Abdominal discomfort while taking a GLP-1 RA or GLP-1/GIP DA has been reported from various causes, including a direct effect of

the drug, biliary complications, gastroparesis, gastritis, constipation, intussusception, and acute pancreatitis.

GLP-1 RA use is associated with abdominal pain, occurring in 10% to 20% of patients, compared with 5% to 10% in placebo groups.²¹ This pain is typically mild, transient, dose-dependent, and nonspecific in location and character. Upper abdominal pain, especially with fever, may suggest biliary complications, which occur at higher rates with GLP-1 RA therapy.²²

The pain of acute pancreatitis is usually severe and is typically reported in the epigastric region or the left upper quadrant of the abdomen; it is typically constant and may radiate to the back, chest, or flanks.²⁰ In GLP-1 RA trials, the diagnostic criteria for acute pancreatitis include “abdominal pain consistent with acute pancreatitis,” without further definition or report of the abdominal site, radiation, or nature.²³

Serum lipase is a more specific marker of acute pancreatitis than amylase. However, lipase concentrations increase in a variety of nonpancreatic diseases, sometimes by more than 3 times normal.²⁰ Even in the absence of acute pancreatitis, GLP-1 RA use is associated with increased pancreatic enzyme levels.^{24,25} At higher dosages, about 3% of people have lipase concentrations more than 3 times the upper limit of the normal reference range.^{24,25}

Gallbladder and Biliary Diseases Cause Abdominal Pain and Acute Pancreatitis

Cholelithiasis, cholecystitis, and biliary disease occur more often with GLP-1 RA treatment.²⁶ Acute cholecystitis presents with abdominal pain and is a differential diagnosis of acute pancreatitis.²⁷ Gallstones and biliary sludge are often causes of acute pancreatitis.²⁰ Therefore, if a person taking a GLP-1 RA presents with abdominal pain, it is imperative to rule out gallbladder and biliary disease as the cause of the pain and, if present, as a cause of acute pancreatitis.

Summary

When taken together, a judgment based on a combination of abdominal pain and elevated lipase concentrations may lead to overdiagnosis of acute pancreatitis among people treated with GLP-1 RAs. It is not surprising, then, that some retrospective cohort studies show a positive relationship between GLP-1 RAs and pancreatitis,²⁷ whereas others do not.²⁸ Meta-analyses of randomized placebo-controlled trials do not confirm this relationship.¹⁸ Therefore, it is imperative that we draw conclusions from randomized placebo-controlled trials rather than from retrospective cohort studies.

Clinical Case Vignettes

Case 1

A 37-year-old woman is referred for a discussion of GLP-1 RA treatment to lose weight. During a routine physical at age 18 years, she was noted to have elevated triglycerides (close to 1000 mg/dL [11.30 mmol/L]). She developed acute pancreatitis in her early 20s when on oral contraceptives. Thereafter, she had many episodes of acute pancreatitis with hypertriglyceridemia until she experienced temporary relief with plasmapheresis, ileal bypass, and vertical banded gastroplasty. After regaining weight, she had recurrent episodes of acute pancreatitis with severe hypertriglyceridemia. She is not currently symptomatic.

On physical examination, her blood pressure is 118/87 mm Hg, pulse rate is 84 beats/min, and temperature is 98.1°F (36.7°C). Her height is 67 in (170.2 cm), and weight is 227.1 lb (103 kg) (BMI = 35.6 kg/m²). She is in no acute distress. The abdomen is mildly and diffusely tender to deep palpation, with no masses. The remaining examination findings are unremarkable.

She wishes to lose weight and wonders whether a GLP-1 RA would be a good option.

Which of the following is the best advice for this patient?

- GLP-1 RAs cause pancreatitis; she has had pancreatitis and should not consider GLP-1 RA therapy
- Although GLP-1 RAs likely do not cause pancreatitis, she has had pancreatitis and should not consider this therapy; an SGLT-2 inhibitor is a better option
- Although GLP-1 RAs likely do not cause pancreatitis, she has had pancreatitis and should not consider this therapy; a DPP-4 inhibitor is a better option
- GLP-1 RA therapy should be considered for her

Answer: D) GLP-1 RA therapy should be considered for her

Several analyses of randomized, placebo-controlled trials demonstrate that GLP-1 RAs are not associated with an increased risk of acute pancreatitis.²⁸ In patients with a history of acute pancreatitis, a recent retrospective cohort study found that GLP-1 RAs are associated with a lower risk of pancreatitis than SGLT-2 inhibitors or DPP-4 inhibitors. Over one year, GLP-1 RAs showed risk reductions of 0.071 (95% CI, -0.085 to -0.057) compared with SGLT-2 inhibitors, and 0.064 (95% CI, -0.080 to -0.048) compared with DPP-4 inhibitors.²⁹

The postprandial rise in triglycerides was completely abolished during GLP-1 infusion in healthy volunteers.³⁰ Patients with lipodystrophy can develop severe hypertriglyceridemia that leads to pancreatitis. In a study of people with lipodystrophy, 1 year of GLP-1 RA therapy significantly reduced triglyceride levels.³¹ Of 26 patients, 1 who was not adherent to GLP-1 RA treatment developed pancreatitis. While adhering to GLP-1 RA therapy, 2 women did not have another episode of acute pancreatitis over 11 and 8 years of follow-up, despite having experienced pancreatitis 6 and 20 years earlier.

A case report suggests that weight loss associated with GLP-1 RA use in people with a history of pancreatitis related to

hypertriglyceridemia reduces the risk of recurrent pancreatitis.³²

Therefore, GLP-1 RA therapy is reasonable for this patient. Close follow-up of triglycerides may be appropriate.

Case 2

A 65-year-old man initiates semaglutide to manage diabetes with coronary heart disease. While 6 months of GLP-1 RA therapy has improved his hemoglobin A_{1c} and led to weight loss (3.3 lb [1.5 kg]), he has also developed hyperamylasemia and hyperlipasemia and semaglutide has been stopped.

Which of the following is the best advice for this patient?

- A. Elevated pancreatic enzyme levels may occur with GLP-1 RAs without pancreatitis, reflecting adaptive pancreatic growth rather than inflammation
- B. Lipase elevation is diagnostic of acute pancreatitis
- C. Lipase elevation by itself is not diagnostic of acute pancreatitis, but reliably predicts which patients will develop acute pancreatitis
- D. Amylase elevation by itself is not diagnostic of acute pancreatitis, but reliably predicts which patients will develop acute pancreatitis

Answer: A) Elevated pancreatic enzyme levels may occur with GLP-1 RAs without pancreatitis, reflecting adaptive pancreatic growth rather than inflammation

GLP-1 RA use is associated with increases in median lipase and pancreatic amylase levels. These changes are not associated with adverse events. For example, within the first 6 months of treatment, liraglutide increases lipase levels 4 times more than the 7% increase with placebo.^{24,25} The elevations are reversible upon discontinuation of the drug. With GLP-1 RA therapy at higher doses, lipase elevations above the upper normal limit of the reference range occur 3 times more often than with placebo, and elevations greater than 3 times

the upper normal limit of the reference range occur 2 times more often than with placebo.^{24,25}

Enzyme elevations have a very low positive-predictive value for acute pancreatitis (<1%),^{24,25} Review of data provides no basis for routine amylase/lipase monitoring during liraglutide treatment except in cases of suspected acute pancreatitis. The enzyme elevations appear to have a pharmacologic effect rather than to act as markers of pancreatic pathology. GLP-1 receptor activation induces signaling pathways in the exocrine pancreas that promote cell growth and concomitant enzyme release, suggesting that increases in amylase and lipase levels in patients treated with GLP-1 RAs reflect adaptive growth rather than early-stage pancreatitis.³³ Histopathological studies in animal models showed no evidence of pancreatitis, inflammation, or structural changes despite enzyme increases.³⁴

Because GLP-1 RA use is associated with abdominal pain and elevated pancreatic enzymes, current diagnostic criteria may misdiagnose a person as having acute pancreatitis caused by a GLP-1 RA.²⁰ The risk of misdiagnosis can be diminished by careful history-taking and examination. Other causes of abdominal pain and pancreatitis, if present, should be ruled out. Abdominal pain and abnormally elevated lipase concentrations normalize with discontinuation of the GLP-1 RA.

Despite the problems as noted above, the diagnostic criteria for acute pancreatitis should not be modified for individuals using GLP-1 RAs, but clinicians should apply the existing criteria with heightened awareness that both abdominal pain and enzyme elevations can occur independently of pancreatitis in this patient population.³⁵

Case 3

A 56-year-old man with obesity (BMI = 38.4 kg/m²) has had T2D for 10 years. After a recent myocardial infarction, GLP-1 RA therapy is being considered both for glycemic control and reduction in atherosclerotic CVD risk. He has an 8-mm IPMN with an average growth rate of less

than 1 mm per year for the last 3 years without an increase in the solid component. The main pancreatic duct diameter is less than 5 mm; there are no mural nodules, no enhancing septations, and no lymphadenopathy. He has no history of pancreatitis or elevated pancreatic enzymes. The CA 19-9 concentration is normal.

Which of the following is the best advice to provide this patient?

- A. Risk of pancreatic carcinoma is very high; GLP-1 RA therapy is contraindicated and should not be considered
- B. Risk of pancreatic carcinoma is low, but GLP-1 RA therapy is contraindicated and should not be considered
- C. Risk of pancreatic carcinoma is high, but GLP-1 RA therapy should be considered
- D. Risk of pancreatic carcinoma is unknown and GLP-1 RA therapy should be considered

Answer: D) Risk of pancreatic carcinoma is unknown and GLP-1 RA therapy should be considered

This patient has low-risk IPMN. High-risk stigmata include obstructive jaundice, a main pancreatic duct diameter ≥ 10 mm, an enhancing mural nodule ≥ 5 mm, and a solid mass. Worrisome features include cyst size ≥ 30 mm, main pancreatic duct diameter 5 to 9.9 mm, an enhancing mural nodule < 5 mm, thickened or enhancing cyst wall or septations, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy, lymphadenopathy, cyst growth rate ≥ 2.5 mm/y, septal nodal structure, elevated CA 19-9, new-onset diabetes, and main duct or mixed-type IPMN.^{36,37}

GLP-1 RA therapy may be cautiously initiated for a patient with a low-risk 0.9-cm IPMN and diabetes without worrisome features, provided routine imaging surveillance continues and the patient is closely monitored. The potential CV and metabolic benefits of GLP-1 RAs outweigh the theoretical risk of IPMN progression in low-risk cases.³⁸

GLP-1 RAs offer significant benefits for this patient's existing conditions. In patients with T2D, long-acting GLP-1 RAs (injectable liraglutide, oral and injectable semaglutide, and injectable dulaglutide) demonstrated a 14% reduction in MACE, 14% reduction in hospitalization for heart failure, and 12% reduction in all-cause mortality across 10 trials involving more than 71,000 patients.³⁹ These agents are specifically indicated for patients with established CVD or multiple CV risk factors.⁴⁰

Pancreatic cysts were not explicitly listed as an exclusion criterion in trials of GLP-1 RAs approved to reduce atherosclerotic CVD events. Data on the direct effect on IPMN progression remain limited and largely theoretical. Although numerous studies and meta-analyses have found no significant correlation between GLP-1 RA therapy and acute pancreatitis or pancreatic cancer in general populations, critical gaps persist regarding their effects, specifically in patients with IPMN, a condition with potential for malignant transformation.⁴¹

Reassuring data from CV outcomes trials and large observational studies show no increased risk of pancreatic malignancy with GLP-1 RAs.⁴¹ Rigorous clinical studies are needed that specifically address this patient population. Until then, shared decision-making with patients with IPMNs should begin with an understanding of the unknown risk posed by IPMN and the use of GLP-1 RAs, as well as the clear CV benefits of these agents.

Key Learning Points

- Up to one-third of people receiving GLP-1 RAs may have elevated pancreatic enzymes. Monitoring pancreatic enzymes as a precaution in people receiving GLP-1 RAs does not help predict pancreatitis.
- A history of pancreatitis is not a contraindication to the use of GLP-1 RAs. People with a history of acute pancreatitis are at higher risk of another episode.

Observational studies and case reports suggest that the risk of acute pancreatitis does not increase with GLP-1 RA use. If GLP-1 RAs reduce the proximate causes of pancreatitis through weight loss and a dramatic reduction in triglycerides, the risk of pancreatitis may decline with their use. This remains to be robustly proven.

- Earlier studies suggested a relationship between GLP-1 RA use and pancreatic malignancy. Several analyses of randomized controlled trials show no increased risk of pancreatic malignancy with GLP-1 RAs. Preexisting pancreatic lesions may pose a variable risk of pancreatic exocrine malignancy. We do not know whether or how GLP-1 RAs affect the risk of pancreatic

malignancy in high-risk individuals. Shared decision-making should incorporate patients' values regarding theoretical pancreatic cancer risks and life expectancy, as well as the expected benefits of weight loss, glycemic control, and reduced cardiorenal events. Multidisciplinary input and ongoing surveillance are essential. This field remains inadequately and robustly explored.

- Risks of pancreatitis and pancreatic cancer are not absolute contraindications to the use of GLP-1 RAs or GLP-1/GIP DA. These agents are contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, during pregnancy and breastfeeding, and in those with hypersensitivity to these agents.

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GENERAL ENDOCRINOLOGY

Hormone Balancing: Addressing Social Media Myths

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Review the nonspecific symptoms and testing protocols proposed for diagnosing the most common pseudoendocrine disorders.
 - Discuss the non-evidence-based and potentially harmful treatments that have been proposed for the most common pseudoendocrine disorders.
 - Develop a practical, personalized, and compassionate approach to the evaluation and management of people with pseudoendocrine disorders.
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Significance of the Clinical Problem

Pseudoendocrine disorders are often self-diagnosed via the internet or by people without medical or health care training, who promote non-evidence-based diagnoses and treatments. Influencers promote many of these myths in the media. People diagnosed with pseudoendocrine disorders frequently present to endocrinologists requesting further evaluation or treatment of these phony disorders with diagnostic or treatment modalities that lack evidence for accuracy, efficacy, or safety, and that may even be significantly harmful.¹⁻⁵

Practice Gaps

- Providers and learners are trained to recognize, diagnose, and treat true endocrine disorders, but have little education or training in how to recognize and manage people who believe they have proposed disorders for which no scientific evidence exists.
- There is little or no education or training on how to avoid or withdraw from non-evidence-based, ineffective, and potentially harmful treatments.
- There is scant training on how to engage in conversations and successfully manage these vulnerable people with the respect and compassion necessary for positive outcomes.

Discussion

In recent times, we have seen a disturbing proliferation of print, internet, and broadcast advertisements and claims about fabricated diseases that lack any actual scientific or credible clinical evidence for their existence and for which unproven and potentially harmful remedies are openly shilled for profit. Practitioners may proclaim themselves experts in hormone therapy without formal training and confidently promote unvalidated hormone evaluations and treatments. Some practitioners make astonishing promises about the benefits of herbal, supplemental, and other unproven therapies that they sell from their offices and/or online. Vulnerable people are being given harmful and even dangerous products that contain porcine whole-organ extracts (most

commonly thyroid and/or adrenal) or hormone injections that produce highly elevated and unsafe levels of sex hormones, especially testosterone, without any concern for short-term safety or long-term outcomes. Often, these products carry surprisingly high costs for people who visit these practitioners and yield no beneficial effects, and may even harm, despite being promised symptom improvement, safety, and full insurance coverage.¹⁻⁵

What is our responsibility, as concerned practitioners and citizens, in the face of these rogue practitioners and practices? We clearly have a primary obligation to protect each of our patients and communities from these unscrupulous, charlatan practitioners and the unproven, costly, and sometimes dangerous treatments they promote. We can do this through one-on-one in-person education with our patients. We can also direct them to credible professional websites, such as those of the Endocrine Society, the American Thyroid Association (ATA), and the Mayo Clinic.

More broadly, we can seek opportunities to bring these issues to the attention of the general public. For example, I was interviewed on a local television station about testosterone therapy; I informed the listeners that low testosterone levels are often a manifestation of more serious underlying medical conditions or medications, that treatment of these conditions should be the primary focus, and that low testosterone levels caused by these conditions are often restored to normal, without a need for lifelong testosterone replacement therapy, if the underlying medical conditions are appropriately managed.

We can encourage our national and local professional organizations (American Medical Association [AMA], American College of Physicians [ACP], the Endocrine Society, the American Association of Clinical Endocrinologists [AACE], the ATA, and state medical societies) to publish fact sheets, official statements, and guidelines regarding these deceptive practices. Finally, we can write editorials and commentaries in local newspapers. A particularly well-written piece by Dr. Lisa Pryor was published in the *New York Times*, entitled “How to Counter the Circus of Pseudoscience.”⁵

Another option is to report rogue practitioners to your state medical board. A small group of Colorado physicians reported a local practitioner who was treating patients complaining of fatigue with a combination of high-dose prednisone and desiccated thyroid extract without testing for adrenal insufficiency (AI) or hypothyroidism before initiating this aggressive therapy. I was asked to testify in court regarding this case. The outcome was the removal of his medical license; he subsequently retired.

Dr. Denis Wilson, who declared “Wilson syndrome” to be a widespread, debilitating, but treatable, disorder, was sanctioned by the Florida Board of Medicine after a 50-year-old woman died of cardiac complications while on excessive amounts of thyroid hormone prescribed by Wilson. In 1992, the Florida Board of Medicine accused him of “fleecing” patients with a “phony diagnosis.” The Board and Wilson agreed to a 6-month suspension of his medical license, after which Wilson agreed to attend 100 hours of continuing medical education, undergo psychological testing, and pay a \$10,000 fine before resuming practice. (State of Florida, Department of Health. February 12, 1992. Final Order Number: DPR9200039ME)

As physicians and health care providers, we have greater influence on these issues than anyone else in our communities. The public listens to us; what we say makes a difference.

Definition of a Pseudoendocrine Disorder

“Pseudoendocrine disorder” lacks a clear definition. Here, the term is used mainly to describe proposed disorders that have never been scientifically proven to exist but that, due to widespread misinformation available on the internet and other media, are relatively commonly diagnosed and treated with equally unproven and sometimes dangerous treatments. Alternatively, “pseudoendocrine disorder” can denote an endocrine diagnosis made in error due to conditions, medications, or supplements that

adversely affect the accuracy of valid endocrine tests. A more complete discussion of all these issues can be found in reference 1.

Case 1

A 47-year-old woman has experienced fatigue for about 15 years but reports progressive “total exhaustion” over the past year. She does not sleep well but does not snore. Her appetite is poor. She eats full meals only occasionally but snacks frequently throughout the day. She experienced mild weight gain (5 lb [2.3 kg]) in the past year. She cannot exercise because of fatigue. She requests treatment for adrenal fatigue, for which she says she has tested positive.

She had mononucleosis at age 18. She occasionally takes prescription pain medication.

On physical examination, her blood pressure is 128/70 mm Hg, and pulse rate is 80 beats/min. Her height is 68 in (172.7 cm), and weight is 157 lb (71.2 kg). Orthostatic vital signs are negative. Examination findings are normal.

A full-day salivary cortisol profile is interpreted to show “adrenal fatigue.”

Question 1: Which of the following persons with significant public influence has promoted unvalidated testing protocols and non-evidence-based treatment for adrenal fatigue?

- A. Anthony Fauci
- B. Donald Trump
- C. Tom Cruise
- D. Dr. Mehmet Oz

Answer: D) Dr. Mehmet Oz

Dr. Mehmet Oz, a neurosurgeon and prominent television personality, invited Dr. Robert Vigersky, MD, then President of the Endocrine Society, to appear on his TV show on October 22, 2015, to debate the evidence for (Dr. Oz) and against (Dr. Vigersky) the validity of adrenal fatigue as an authentic medical condition. Dr. Vigersky made strong, convincing arguments against the existence of adrenal fatigue. Dr. Oz

argued strongly, without valid scientific evidence, in support of adrenal fatigue as a true condition and offered treatment advice for people who think they may have adrenal fatigue.

Question 2: What is the most potentially harmful treatment proposed for adrenal fatigue?

- A. Healthy diet, regular exercise, good sleep habits, and stress reduction
- B. Adrenal extracts, which may cause central AI
- C. Licorice root, which may cause hypertension
- D. Loss of trust in providers who do not diagnose or treat adrenal fatigue

Answer: B) Adrenal extracts, which may cause central AI

One proposed treatment for “adrenal fatigue” is “adrenal support” supplements containing extracts from animal adrenal glands. These supplements contain actual steroid hormones, in unknown amounts, that can suppress the hypothalamic-pituitary-adrenal axis, causing secondary AI. This condition can be life-threatening if not recognized and treated during critical or even moderate systemic illnesses. Recommending a healthy diet, regular exercise, good sleep habits, and stress reduction are all beneficial measures and certainly not harmful. Consumption of licorice root, which has variable mineralocorticoid activity, can cause hypertension; while concerning, this is not the most harmful of the listed choices. Loss of trust in a provider usually does not occur when the provider is honest with patients and gives them the respect and attention they deserve.

What Is Adrenal Fatigue?

Adrenal fatigue was first proposed by James L. Wilson, PhD, in his 2001 book *Adrenal Fatigue: The 21st Century Stress Syndrome*. Wilson suggested that adrenal fatigue develops when the adrenal glands become exhausted and unable to produce adequate amounts of adrenal hormones to cope with daily stressors. It was said to occur in people experiencing chronic high stress (mental,

emotional, or physical) in their work and/or family life. Adrenal fatigue is characterized by nonspecific symptoms, including fatigue, sleep disturbances, difficulty coping, body aches, digestive problems, and dependence on caffeine. Numerous practitioners and websites falsely promote this pseudoendocrine condition and its proposed treatments. Adrenal fatigue was featured on Dr. Oz's show on October 22, 2015.

How Is Adrenal Fatigue Diagnosed?

Affected people are encouraged to self-diagnose adrenal fatigue based solely on symptom-scoring systems available on the internet. Providers or patients themselves can also order a salivary cortisol profile, in which multiple salivary cortisol samples are collected over the course of a day and sent to a lab for analysis (for a price). If salivary cortisol levels fall below a normative line, the diagnosis of adrenal fatigue is said to be confirmed.^{1,6}

Is Adrenal Fatigue a Real Condition?

Adrenal fatigue has never been scientifically proven to exist.^{1,6-8} Symptom-scoring systems or salivary cortisol profiles have never been tested scientifically or validated as tools to accurately evaluate hypothalamic-pituitary-adrenal function. As clinician-scientists, we must be open to novel ideas and proposals. But rigorous verification by well-designed, well-conducted scientific investigations must still be the standard by which we evaluate and clinically apply new and innovative ideas. It is not sufficient, when patients' health and well-being are concerned, to simply propose a hypothesis and apply it without diligent scientific investigation.^{1,6-8}

There are validated, widely accepted, and mostly accurate tests for actual AI: low baseline serum cortisol levels ($<3 \mu\text{g/dL}$ or $<2 \mu\text{g/dL}$ [in recent more sensitive assays]) and low ACTH (cosyntropin)-stimulated cortisol levels ($<18 \mu\text{g/dL}$ or $<15 \mu\text{g/dL}$ [in recent more sensitive assays]).⁹ While accuracy is good (not perfect) for diagnosing primary AI, the diagnostic accuracy for secondary (central) AI is clearly not optimal.¹⁰ We still

have much to learn about the best tests to assess complete and partial primary and secondary AI and the optimal treatment strategies. Nonetheless, we must not be deceived into accepting and acting on the results of unvalidated tests, or into recommending or prescribing non-evidence-based and potentially dangerous treatments.

How Is Adrenal Fatigue Treated?

Proposed treatments start with a healthy, well-balanced diet, regular exercise, good sleep habits, stress reduction, and cessation of smoking and alcohol use.¹¹ Most of us would agree with these measures; this advice is appropriate for almost everyone. But adrenal fatigue websites and promoters also suggest the use of reflexology, licorice root, or a variety of supplements (vitamins, minerals, amino acids) that are claimed to improve adrenal function (without documented evidence). However, much more concerning are the recommendations for and links to purchase "real" or "raw" adrenal extracts from bovine adrenal glands.¹² The obvious potential for these products to cause secondary AI is clearly a major safety concern. If unrecognized, secondary AI can be a life-threatening condition, especially in the setting of other critical or even moderate systemic illnesses. It is important to recognize that many patients with chronic fatigue take opioids, which can also cause secondary AI.¹³

What Measures Have Been Taken to Educate the Public About the Adrenal Fatigue Myth?

The Endocrine Society has taken the lead in opposing the promotion of adrenal fatigue.⁷ The website and printed literature provide clear warnings, such as "No scientific proof exists to support adrenal fatigue as a true medical condition"; "Doctors are concerned that if you are told you have this condition, the real cause of your symptoms may not be found and treated correctly"; "Doctors urge you not to waste precious time accepting an unproven diagnosis such as 'adrenal

fatigue' if you feel tired, weak, or depressed. If you have these symptoms, you may have AI, depression, obstructive sleep apnea, or other health problems. Getting a real diagnosis is very important to help you feel better and overcome your health problem," and "If you take adrenal hormone supplements when you don't need them, your adrenal glands may stop working and become unable to make the hormones you need when you are under physical stress. When these supplements are stopped, a person's adrenal glands can remain 'asleep' for months. People with this problem may be in danger of developing a life-threatening condition called adrenal crisis."

The Mayo Clinic website also has the following strong statements⁸: "The term often shows up in popular health books and on alternative medicine websites, but it isn't an accepted medical diagnosis"; and "It's frustrating to have persistent symptoms your doctor can't readily explain. But accepting a medically unrecognized diagnosis from an unqualified practitioner could be worse. Unproven remedies for so-called adrenal fatigue may leave you feeling sicker, while the real cause—such as depression or fibromyalgia—continues to take its toll."

Case 2

A 38-year-old woman is self-referred for hormone evaluation because of progressive fatigue since age 28. She also notes hair loss, weight gain, and "brain fog." She is adamant that this is not depression. She ordered tests online and wants answers and help. Her medical history is unremarkable. Her only medication is a daily multivitamin.

On physical examination, her blood pressure is 129/74 mm Hg, and pulse rate is 74 beats/min. Her height is 67 in (170.2 cm), and weight is 158 lb (71.7 kg) (BMI = 24.8 kg/m²). Examination findings are normal, including the thyroid gland and skin.

Her questions, based on the online tests she ordered, include: Do I have "Wilson syndrome" or "reverse T₃ syndrome"? Why can't I make T₃? Will you help me?

Laboratory test results:

TSH = 2.1 mIU/L (0.45-4.5 mIU/L)
 Free T₄ = 1.0 ng/dL (0.78-1.81 ng/dL)
 (SI: 12.87 pmol/L [10.04-23.30 pmol/L])
 Free T₃ = 2.4 pg/mL (2.3-4.2 pg/mL)
 (SI: 3.69 pmol/L [3.53-6.45 pmol/L])
 Reverse T₃ = 23 ng/dL (10-24 ng/dL)
 (SI: 0.35 nmol/L [0.15-0.37 nmol/L])
 TPO antibodies, negative
 Thyroglobulin antibodies, negative

Question 3: What is the proposed unvalidated pathophysiology of Wilson syndrome?

- Decreased T₄-to-T₃ conversion due to genetics and/or life experiences
- Increased T₃-to-T₂ conversion due to genetics and/or life experiences
- Tissue thyroid hormone resistance due to genetics and/or life experiences
- Increased albumin affinity for T₄ and T₃ due to genetics and/or life experiences

Answer: A) Decreased T₄-to-T₃ conversion due to genetics and/or life experiences

The proposed underpinning of the pseudoendocrine disorder "Wilson syndrome" is an acquired impairment in the conversion of the prohormone T₄ into the active thyroid hormone T₃, due to stressful life circumstances, possibly superimposed on a genetic or epigenetic background.¹⁴ There is no actual evidence for this pathophysiology or for the existence of this syndrome. There have been no proposals or evidence that these individuals have impaired T₃-to-T₂ conversion, thyroid hormone resistance, or high albumin affinity for T₄ or T₃.

Question 4: What is the unvalidated proposed pathophysiology of reverse T₃ syndrome?

- Increased reverse T₃ increases hepatic T₃ metabolism
- Increased reverse T₃ competes with T₃ for binding to the thyroid hormone receptor
- Increased reverse T₃ suppresses TSH synthesis and secretion by the pituitary gland
- Increased reverse T₃ increases hepatic cortisol metabolism

Answer: B) Increased reverse T_3 competes with T_3 for binding to the thyroid hormone receptor

The proposed cause of the pseudoendocrine disorder “reverse T_3 syndrome” is impaired T_4 -to- T_3 conversion, which not only results in low serum T_3 levels but also produces high reverse T_3 levels that compete with T_3 for binding to thyroid hormone receptors, thereby further decreasing T_3 action.¹⁵ The well-documented fact that T_3 has a 100-fold higher affinity for the T_3 receptor than does reverse T_3 ¹⁶ indicates that reverse T_3 cannot outcompete T_3 for occupancy of the T_3 receptor. There have been no proposals or evidence that reverse T_3 increases hepatic T_3 metabolism, suppresses TSH synthesis or secretion, or increases hepatic cortisol metabolism.

What Is Wilson Syndrome?

Wilson syndrome was proposed by Dr. E. Denis Wilson, humbly named after himself, in 1990. Wilson syndrome is suggested to be present when people develop chronically impaired conversion of T_4 to T_3 as a prosurvival adaptation in response to stress.^{1,14} Susceptible people include famine survivors or their descendants (Scotch, Irish, Russian, Native American); holocaust survivors or their descendants; survivors of divorce, death of a loved one, or stress (family or job); chronic dieters; yeast sufferers; and people with hypoglycemia, eating disorders, and sleep disorders. The diagnosis is said to be made by taking axillary temperature with a mercury thermometer every 3 hours, starting 3 hours after waking, and averaging the readings over several normal days. If the mean body temperature is 1 or more degree below normal, the person “may” have Wilson syndrome.¹⁴ The diagnosis does not involve testing TSH or thyroid hormone levels.^{1,14}

What Is the Proposed Treatment for Wilson Syndrome?

The suggested treatment for Wilson syndrome involves cycling body temperature to normal with “proper T_3 thyroid supplements” (doses up to

100 mcg daily), then cycling it back down again. The cycle is repeated until the body temperature remains normal after stopping T_3 supplements; this typically takes 3 to 4 cycles, but may require 11 to 12 cycles in difficult cases.^{1,14}

What Measures Have Been Taken to Educate the Public About the Myth of Wilson Syndrome?

A 50-year-old woman died of an arrhythmia and heart attack while on amounts of thyroid hormone prescribed by Wilson; the Florida Board of Medicine accused him of “fleecing” patients with a “phony diagnosis.” The Board and Wilson agreed to a 6-month suspension of his medical license, after which Wilson agreed to complete 100 hours of continuing medical education, undergo psychological testing, and pay a \$10,000 fine.

The ATA states emphatically (website) that there is no scientific evidence to support the existence of Wilson syndrome and that the proposed treatment is unsafe and frankly dangerous.¹⁷

How Is Reverse T_3 Syndrome Different From Wilson Syndrome?

Reverse T_3 syndrome, which is similar to Wilson syndrome, was proposed in a 2016 book and website “Stop the Thyroid Madness.”¹⁵ The proposal was that impaired T_4 -to- T_3 conversion not only reduces serum T_3 levels but that T_4 is diverted into excess reverse T_3 that then competes with T_3 for binding to the T_3 receptor, further reducing peripheral tissue access to T_3 action. Not only is there no scientific evidence supporting the existence of this condition, but there is also well-documented, published evidence that T_3 has a 100-fold higher affinity for the thyroid hormone receptor than reverse T_3 ; therefore, an excess of reverse T_3 cannot impair T_3 binding.¹⁶ The book and website also propose ways to “flush reverse T_3 out of the body” with lifestyle measures and taking liothyronine.¹⁵ None of these proposed treatments is evidence-based.

Case 3

A 65-year-old man emails through the patient portal (no visits for the past 6 years): “Recently, I increased my thyroid dose from 200 to 300 mcg daily due to fatigue. I feel better. Please renew my prescription for 300 mcg. By the way, I read on the internet that low-dose naltrexone can cure Hashimoto thyroiditis. My naturopath agreed. Please call in a prescription for that also.”

Question 5: The proposed mechanism for the beneficial effects claimed for low-dose naltrexone (LDN) is that it does which of the following?

- A. Increases the serum testosterone-to-estradiol ratio
- B. Increases the serum and tissue cortisol-to-aldoosterone ratio
- C. Increases the serum and tissue T₃-to-T₄ ratio
- D. May suppress autoimmunity

Answer: D) May suppress autoimmunity

Because proopiomelanocortin (POMC) metabolites (including endogenous opioids) may have some immune-regulatory effects, it was proposed, not proven, that LDN can suppress autoimmunity. LDN does not affect any of the above hormone ratios (Answers A, B, and C).

Question 6: What autoimmune or idiopathic disorders have been shown to benefit from LDN?

- A. Hashimoto thyroiditis
- B. Multiple sclerosis
- C. Parkinson disease
- D. None

Answer: D) None

There is no evidence that LDN has any beneficial effects on autoimmune, neoplastic, and neurodegenerative disorders, including Hashimoto thyroiditis, multiple sclerosis, or Parkinson disease.

What Is the Rationale Behind LDN Therapy?

The notion that endogenous opioids and opioid antagonists may play a role in healing and tissue repair led to the use of LDN as a possible treatment for numerous disorders. Dr. Bernard Bihari, “a LDN Pioneer and Champion,” is featured in a 2002 online video describing his LDN work; an online tribute credits him with improving the lives and relieving symptoms in “tens of thousands (some say hundreds of thousands) of people with multiple sclerosis, rheumatoid arthritis, lupus, HIV/AIDS, autoimmune thyroid disease and even cancer.” In her book *Honest Medicine*, Julia Schopick proposes LDN as an “effective, time-tested, inexpensive treatment for life-threatening diseases,” including “multiple sclerosis, epilepsy, liver disease, lupus, rheumatoid arthritis, and other disorders.”

What Evidence Supports the Efficacy of LDN?

A 2007 study published in the *American Journal of Gastroenterology* reported improvements in the Crohn Disease Activity Index during 12 weeks of LDN treatment and for 4 weeks after stopping the medication in patients with active Crohn disease.¹⁸ Other studies followed with mixed results. A 2018 Cochrane Database Systematic Review concluded there is “insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN for patients with active Crohn’s disease.”¹⁹ There is no valid evidence to support the use of LDN to treat autoimmune endocrine disorders.¹

Is Low Testosterone a Validated Clinical Condition in Women? Should It Be Treated?

Dr. Susan R. Davis, in her address to the 2025 Annual Meeting of The Menopause Society, stated: “There is no level below which we would say a testosterone level is too low, and there is no established androgen deficiency syndrome in women. This means that there are no health conditions that we can link to low levels of

testosterone, there is no medical concern with lower levels, and 'low levels' do not need replacement. It is not appropriate to measure testosterone when women have symptoms, such as fatigue or depression, because a 'low' level just doesn't tell us anything."

In 2019, an international panel issued a global consensus position statement on testosterone therapy for women, concluding that "the only evidence-based indication for testosterone therapy for women is for the treatment of hypoactive sexual desire disorder (HSDD), with available data supporting a moderate therapeutic effect. There are insufficient data to support the use of testosterone for the treatment of any other symptom or clinical condition, or for disease prevention."²⁰ The statement was endorsed by 12 major organizations, including the International Menopause Society, the Endocrine Society, and the European Menopause and Andropause Society.²⁰

What Conditions or Situations Can Result in an Erroneous Diagnosis of an Endocrine Disorder?

Pseudo-Cushing Syndrome

Pseudo-Cushing syndrome results from nonneoplastic conditions that activate the hypothalamic-pituitary-adrenal axis and can produce hypercortisolism and cushingoid features.^{21,22} These conditions include alcoholism, depression, and poorly controlled diabetes. The usual screening tests for Cushing syndrome (24-hour urinary cortisol measurement, 1-mg overnight dexamethasone-suppression test, bedtime salivary cortisol measurement) can all be positive in people with these conditions. However, adequate treatment of the disorders usually resolves hypercortisolism. Class 3 obesity can also have many features suggestive of Cushing syndrome. However, selective central obesity, proximal muscle weakness, bruising, and violaceous striae are usually absent in class 3 obesity, and 24-hour urinary cortisol excretion is usually normal.

Estrogen in women taking oral contraceptive pills and those who are pregnant promotes increased hepatic production of cortisol-binding globulin, which binds cortisol for transport in the circulation.²³ Serum total cortisol levels are increased approximately 67% in women who take oral contraceptive pills; pregnancy can cause similar elevations. This elevation can cause false-positive results for both baseline and dexamethasone-suppressed serum cortisol levels. Tests that measure free cortisol (urinary free cortisol, salivary free cortisol) are not affected by oral contraceptive pills or pregnancy.

Pseudopheochromocytoma

Pseudopheochromocytoma is a term used to describe symptoms resembling those of pheochromocytomas, including anxiety, tremors, palpitations, headaches, and sometimes hypertension, despite normal serum and urinary catecholamine and metabolite levels.²⁴ Appropriate management of pseudopheochromocytoma is to provide reassurance. The term pseudopheochromocytoma also applies to 2 situations in which catecholamines are actually elevated. In hospitalized patients (in the intensive care unit and nonintensive care unit settings), urinary metanephrine and normetanephrine levels can be markedly elevated, with significant overlap with those seen in pheochromocytomas and paragangliomas.²⁵⁻²⁷ Therefore, elevated catecholamines and metabolites should be interpreted with caution in the setting of severe illness or hospitalization. Also, the use of levodopa/carbidopa for Parkinson disease significantly elevates plasma and urine dopamine levels without affecting norepinephrine or epinephrine.^{28,29}

Biotin Interference With Hormone Assays

Biotin is a reagent component in immunoassays for many hormones. People taking high-dose biotin supplements (5000-20,000 mcg daily for hair loss and brittle nails) can have falsely abnormal hormone measurements.^{30,31} High biotin concentrations can falsely elevate free T₄, free T₃, TRAb, cortisol, testosterone, and estradiol in

biotin-streptavidin competitive immunoassays and falsely lower TSH, PTH, ACTH, LH, and FSH in biotin-streptavidin immunometric assays. Graves disease can thus be erroneously diagnosed (low TSH, high free T_4 and T_3 , positive TRAb) in someone taking high-dose biotin. An 8-hour abstinence from biotin often corrects this anomaly, but most authorities recommend 3 or more days of abstinence.

Macro-TSH Interference With Hormone Assays

Macro-TSH refers to the presence of large TSH-autoantibody molecular complexes, which most often occur in the context of other autoimmune diseases. Macro-TSH is characterized by elevated (often markedly) TSH with normal serum free T_4 levels. This condition can be detected by gel filtration chromatography or polyethylene glycol (PEG) precipitation.^{32,33}

Human Antimouse Antibody (Heterophile Antibody) Interference With Hormone Assays

Human antimouse antibodies (HAMA) (heterophile antibodies) can interfere with accurate measurement of serum hormone concentrations.³⁴ HAMA occur when humans exposed to mouse antigens (lab workers, farm workers, people experiencing homelessness, etc) develop antibodies against mouse antibodies. Since mouse antibodies are used as capture antibodies in many hormone immunoassays, HAMA can bind to them and interfere with accurate hormone measurements. For example, serum TSH levels may be elevated in the presence of normal or elevated free T_4 levels, creating significant diagnostic challenges. Labs can be notified that HAMA may be present and asked to measure HAMA and/or use liquid chromatography–tandem mass spectrometry or a specific radioimmunoassay to avoid this interference.

Describe a Reasonable, Compassionate, Patient-Centric Approach to People Who Present With Symptoms Erroneously Attributed to a Pseudoendocrine Diagnosis

All providers will develop their own personalized approach that works best for their patients, but I find it best to always remember 3 crucial points: (1) The patient is not to blame for their diagnosis; like all others, they deserve our full attention and compassion; (2) The patient's quality of life is poor, and they are frustrated; (3) It is an honor that they entrust you/me with an opportunity to help them achieve better health and quality of life.

I listen attentively, perform a good physical examination, and offer additional testing if appropriate. I explore nonendocrine and psychiatric contributors to their symptoms. I understand and acknowledge that current testing options do have some limitations. I recommend good nutrition, regular exercise, good sleep habits, and stress reduction for all patients. And I always provide honesty, encouragement, and compassion.^{1,11}

Key Learning Points

- Largely due to the internet and some celebrities, there has been a proliferation of proposed, unvalidated endocrine disorders with unproven diagnostic criteria and non-evidence-based, sometimes dangerous treatment recommendations.
- Adrenal fatigue, Wilson syndrome, and reverse T_3 syndrome are examples of these pseudoendocrine disorders with highly nonspecific symptoms, vague diagnostic criteria, and treatments, such as animal whole adrenal extracts and high-dosage liothyronine, that can significantly harm patients.
- Patients who present claiming to have these conditions should not be blamed for being duped by unscrupulous individuals and websites; they should be treated with respect, patience, honesty, and compassion.

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NEUROENDOCRINOLOGY AND PITUITARY

Ectopic Cushing Syndrome

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify clinical and biochemical features suggestive of ectopic Cushing syndrome (ECS).
- Differentiate ectopic ACTH secretion from pituitary Cushing disease using dynamic testing and imaging.
- Manage severe hypercortisolism in patients with ECS, including selection of medical therapy, surgery, and bilateral adrenalectomy.

Significance of the Clinical Problem

ECS is a rare but life-threatening cause of endogenous hypercortisolism, accounting for approximately 5% to 10% of cases of ACTH-dependent Cushing syndrome.¹⁻³ Affected individuals often present with rapidly progressive and severe hypercortisolism, leading to profound metabolic derangements, opportunistic infections, thromboembolism, cardiovascular events, and excess mortality.⁴⁻⁶ Unlike pituitary Cushing disease, ECS is characterized by marked heterogeneity in clinical presentation, tumor biology, and disease trajectory. While some patients exhibit classic cushingoid features, others present with catabolic manifestations, such as weight loss, muscle wasting, hypokalemia, and acute metabolic decompensation, particularly in the setting of aggressive or metastatic malignancy.^{2,4,7,8} Diagnostic evaluation is further complicated by overlapping biochemical profiles with pituitary disease, imperfect performance of

dynamic endocrine tests, and frequent challenges in localizing the ectopic ACTH source despite advanced imaging techniques.⁹⁻¹³

Historically, evidence guiding ECS management has been limited to small retrospective series and single-center experiences, with the largest early cohorts comprising fewer than 150 patients.^{2,4,7-9,11,14,15} Although these studies established foundational principles of diagnosis and management, they were limited by referral bias, heterogeneity in testing strategies, and evolving imaging and therapeutic options.

Practice Gaps

- Delayed diagnosis due to underrecognition of clinical presentations of ECS.
- Uncertainty in differentiating ectopic ACTH secretion from pituitary Cushing disease when biochemical and imaging results are discordant.
- Inconsistent or delayed management strategies for severe hypercortisolism.
- Limited awareness of prognostic factors associated with complications and mortality in ECS.

Discussion

Overview and Pathophysiology

ECS results from ACTH secretion by tumors located outside pituitary gland, leading to adrenal cortisol excess. Although ECS accounts for a minority of ACTH-dependent Cushing syndrome cases, it is disproportionately associated with severe biochemical hypercortisolism, rapid clinical deterioration, and excess mortality compared with

pituitary Cushing syndrome (Cushing disease).^{4-6,15} Tumors causing ECS are heterogeneous in origin and biological behavior, ranging from indolent neuroendocrine tumors to highly aggressive carcinomas.⁵

Pulmonary neuroendocrine tumors are consistently reported as the most common source of ectopic ACTH secretion, followed by pancreatic neuroendocrine tumors, small cell lung carcinoma, thymic neuroendocrine tumors, and medullary thyroid carcinoma.^{4,5,7,8,11}

Clinical and Biochemical Presentation

Patients with ECS often present with more severe biochemical hypercortisolism than those with pituitary Cushing disease, frequently accompanied by hypokalemia, hypertension, hyperglycemia, and proximal muscle weakness.^{4,5,16} At high concentrations, cortisol overwhelms renal 11 β -hydroxysteroid dehydrogenase type 2, allowing cortisol to activate the mineralocorticoid receptor, and resulting in renal potassium wasting, sodium retention, and hypertension, thus explaining hypokalemia in patients with severe ECS.¹⁷

Clinical presentation of patients with ECS is heterogeneous. While some patients develop classic cushingoid features, others present with catabolic manifestations, such as weight loss, muscle wasting, infections, or thromboembolic events.^{4,5,16} This variability is likely reflective of the differences in the degree and duration of cortisol excess. Patients with aggressive or metastatic malignancies may have insufficient time to develop the phenotypic features of chronic hypercortisolism, despite markedly elevated cortisol levels.

Diagnostic Challenges

Differentiating ECS from pituitary Cushing disease can be challenging. Biochemical overlap between the 2 conditions is common, and no single dynamic test reliably distinguishes them.^{9,10} High-dose dexamethasone-suppression testing and corticotropin-releasing hormone stimulation

may be informative but demonstrate imperfect sensitivity and specificity.^{9,10}

Inferior petrosal sinus sampling is considered the reference standard when noninvasive testing is inconclusive; however, false-negative and false-positive results occur due to technical factors, venous anatomy, or tumor biology.^{12,13} Consequently, diagnostic interpretation must integrate biochemical testing, imaging findings, and clinical context rather than rely on a single modality.

Localization of the ectopic ACTH source is frequently difficult. Cross-sectional imaging may fail to identify small or occult tumors, and discordance between anatomical and functional imaging is common.^{11,14} Functional imaging, including somatostatin receptor-based positron emission tomography, has improved the detection of neuroendocrine tumors but does not eliminate the challenge of diagnosing occult ECS.¹⁴

Management of Hypercortisolism

The cornerstone of ECS management is rapid and effective control of cortisol excess, given the strong association between ongoing hypercortisolism and morbidity and mortality.^{5,6,10} When the ectopic ACTH-secreting tumor is localized and surgically resectable, tumor excision is the preferred definitive therapy and usually results in a cure.⁷

Unfortunately, many patients present with unresectable or metastatic disease, necessitating alternative strategies. Medical therapy with agents targeting cortisol synthesis or action is often initiated as first-line treatment, particularly in patients with metastatic or occult disease. However, achieving complete biochemical control is frequently difficult with medical therapy alone.^{4,5,7-10} Bilateral adrenalectomy provides immediate and definitive control of hypercortisolism and has long been recognized as a life-saving option in patients with severe ECS.^{6,10,15} Accumulating evidence suggests that bilateral adrenalectomy should be considered earlier in selected patients with refractory or rapidly

progressive disease, particularly when definitive tumor-directed therapy is not feasible.¹⁵

Complications and Mortality

ECS is associated with a high burden of complications, including opportunistic infections, venous thromboembolism, cardiovascular events, fractures, and metabolic decompensation.^{4,5,10} These complications often develop early in the disease course and may occur even before a definitive diagnosis is established.

Mortality in ECS remains substantial and is higher than in pituitary Cushing disease.^{5,6} Both tumor-related factors and complications of hypercortisolism contribute to adverse outcomes. Prior cohorts have demonstrated that uncontrolled cortisol excess is a major driver of mortality, emphasizing the importance of early and effective biochemical control.^{4,5}

Clinical Implications

ECS represents a medical emergency requiring prompt recognition, careful diagnostic evaluation, and aggressive management. The heterogeneity of presentation and frequent diagnostic uncertainty necessitate a multidisciplinary approach integrating endocrinology, oncology, radiology, and surgery. Given the limitations of available diagnostic tests and therapies, clinical judgment remains central to optimizing outcomes in this high-risk population.

Clinical Case Vignettes

Case 1

A 54-year-old woman presents with 3 months of progressive proximal muscle weakness, new-onset hyperglycemia, hypertension, and hypokalemia requiring supplementation. She reports easy bruising and facial rounding but has unintentionally lost 11 lb (5 kg). Laboratory evaluation confirms hypercortisolism with elevated late-night salivary cortisol on 2 occasions and markedly elevated 24-hour urinary free cortisol excretion.

Laboratory test results:

Plasma ACTH = 145 pg/mL (7-60 pg/mL)
(SI: 31.9 pmol/L [1.5-13.2 pmol/L])

Morning serum total cortisol =
28 µg/dL (5-21 µg/dL) (SI: 772.5 nmol/L
[137.9-579.3 nmol/L])

Late-night salivary cortisol = 0.8 µg/dL (<0.1 µg/dL)
(SI: 22.1 nmol/L [<2.8 nmol/L])

Post-1 mg dexamethasone cortisol = 25 µg/dL
(<1.8 µg/dL) (SI: 689.7 nmol/L [<49.7 nmol/L])

Post-8 mg dexamethasone cortisol = 27 µg/dL
(<1.0 µg/dL) (SI: 744.9 nmol/L [<27.6 nmol/L])

Urinary free cortisol = 870 µg/24 h (<45 µg/24 h)
(SI: 2401 nmol/d [<124 nmol/d])

Serum potassium = 3.2 mEq/L (3.5-5.2 mEq/L)
(SI: 3.2 mmol/L [3.5-5.2 mmol/L])

Pituitary MRI shows a 4-mm hypoenhancing lesion.

Which of the following is the most appropriate next diagnostic step?

- A. Transsphenoidal pituitary surgery
- B. Inferior petrosal sinus sampling
- C. Pituitary MRI with dynamic contrast
- D. Medical therapy with a steroidogenesis inhibitor
- E. Full-body cross-sectional imaging

Answer: B) Inferior petrosal sinus sampling

Inferior petrosal sinus sampling (Answer B) is indicated when biochemical testing and imaging are discordant or equivocal.¹⁰ Surgery (Answer A) should not proceed without confirmation of the pituitary ACTH source, especially in a patient whose clinical presentation is abrupt and severe, uncharacteristic of Cushing disease. Repeating MRI (Answer C) is unlikely to clarify the ACTH source, especially because the pituitary lesion is already clearly visible. Medical therapy with a steroidogenesis inhibitor (Answer D) is incorrect, as the diagnosis is not yet established. However, this could be an option in situations when diagnostic tests are delayed. Full-body cross-sectional imaging (Answer E) is incorrect because the subtype of ACTH-dependent hypercortisolism is not yet established.

Case 2

A 46-year-old man presents with severe hypokalemia, resistant hypertension, hyperglycemia, and recurrent infections.

Biochemical testing confirms ACTH-dependent hypercortisolism:

Plasma ACTH = 220 pg/mL (7-60 pg/mL)
(SI: 48.4 pmol/L [1.5-13.2 pmol/L])
Morning serum total cortisol =
52 µg/dL (5-21 µg/dL) (SI: 1434.6 nmol/L
[137.9-579.3 nmol/L])
Late-night salivary cortisol = 1.8 µg/dL (<0.1 µg/dL)
(SI: 49.7 nmol/L [<2.8 nmol/L])
Post-1 mg dexamethasone cortisol = 48 µg/dL
(<1.8 µg/dL) (SI: 1324.2 nmol/L [<49.7 nmol/L])
Urinary free cortisol = 980 µg/24 h (<45 µg/24 h)
(SI: 2705 nmol/d [<124 nmol/d])
Serum potassium = 3.0 mEq/L (3.5-5.2 mEq/L)
(SI: 3.0 mmol/L [3.5-5.2 mmol/L])

MRI of the pituitary gland demonstrates a possible 2-mm pituitary adenoma. Inferior petrosal sinus sampling does not demonstrate a central ACTH gradient. Findings on contrast-enhanced CT of the chest and abdomen are unremarkable. Ga-68 DOTATATE PET-CT reveals focal uptake in the pancreatic tail.

Which of the following is the most appropriate next diagnostic step?

- A. Recommend no further testing
- B. Proceed with endoscopic ultrasonography
- C. Repeat cross-sectional imaging in 6 months
- D. Proceed with FDG PET-CT
- E. Repeat inferior petrosal sinus sampling

Answer: B) Proceed with endoscopic ultrasonography

As functional imaging demonstrated uptake in the pancreas, one of the potential locations for ECS, proceeding with a more accurate localization technique, such as endoscopic ultrasonography (Answer B), is the best next step. Abdominal CT is not an accurate test to detect certain pancreatic lesions. Waiting to repeat cross-sectional imaging in 6 months (Answer C) would delay diagnosis and management. Gallium 68 DOTATATE PET is a

more accurate functional imaging than FDG PET-CT (Answer D) for neuroendocrine tumors, and ⁶⁸Ga DOTATATE PET has already demonstrated pancreatic uptake. There is no reason to distrust the conclusion of the ECS subtype, so repeating inferior petrosal sinus sampling (Answer E) is incorrect.

Case 3

A 62-year-old man with newly diagnosed metastatic small cell lung carcinoma presents with profound muscle weakness, hypokalemia, uncontrolled diabetes, and sepsis from pneumonia.

Laboratory test results:

Plasma ACTH = 189 pg/mL (7-60 pg/mL)
(SI: 41.6 pmol/L [1.5-13.2 pmol/L])
Morning serum total cortisol =
78 µg/dL (5-21 µg/dL) (SI: 2151.9 nmol/L
[137.9-579.3 nmol/L])
Urinary free cortisol = 3650 µg/24 h (<45 µg/24 h)
(SI: 10,074 nmol/d [<124 nmol/d])
Serum potassium = 2.4 mEq/L (3.5-5.2 mEq/L)
(SI: 2.4 mmol/L [3.5-5.2 mmol/L])

Despite initiation of a steroidogenesis inhibitor (metyrapone, 1000 mg every 6 hours), cortisol levels remain elevated, and his clinical condition continues to deteriorate. The oncologic team anticipates that systemic cancer therapy will be delayed due to the instability of his condition.

Which of the following is the best next step to control this patient's hypercortisolism?

- A. Add another oral steroidogenesis inhibitor (ie, combination therapy)
- B. Treat metastatic lesions with radiation
- C. Perform bilateral adrenalectomy
- D. Start etomidate therapy and admit to the intensive care unit until chemotherapy initiation
- E. Continue current medical therapy and add antibacterial prophylaxis and anticoagulation

Answer: C) Perform bilateral adrenalectomy

Bilateral adrenalectomy provides immediate and definitive control of cortisol. Adding another

oral steroidogenesis inhibitor (Answer A) or radiation therapy to metastatic lesions (Answer B) is unlikely to control hypercortisolism in a timely manner or achieve complete remission. Etomidate therapy (Answer D) would effectively control hypercortisolism but requires intensive care unit admission and is not a sustainable long-term solution, especially because chemotherapy would not effectively control hypercortisolism. Although urgent initiation of antibacterial prophylaxis and anticoagulation (Answer E) is indicated, this approach would not prevent all complications of suboptimally treated hypercortisolism.

Key Learning Points

- ECS is a medical emergency characterized by severe, often rapidly progressive hypercortisolism with high rates of metabolic complications, infections, thromboembolism, cardiovascular events, and excess mortality.
- Hypokalemia is a hallmark biochemical feature of ECS, reflecting cortisol-mediated activation of the mineralocorticoid receptor at high cortisol concentrations due to saturation of renal 11β -hydroxysteroid dehydrogenase type 2.
- Differentiating ECS from pituitary Cushing disease is frequently challenging and requires integration of biochemical testing, dynamic endocrine tests, imaging studies, and clinical context, as no single diagnostic modality is definitive.
- Medical therapy alone often fails to achieve sustained biochemical control in ECS, with many patients experiencing incomplete or transient responses, necessitating escalation to definitive interventions.
- Rapid and effective control of cortisol excess is the most important modifiable determinant of outcomes, and bilateral adrenalectomy should be strongly considered when tumor-directed therapy is not feasible or when medical therapy fails to provide timely control.

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Neuroendocrine Adverse Effects of Cancer Treatment: Immune Checkpoint Inhibitors

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Recognize clinical presentations of immune checkpoint inhibitor (ICI)-associated hypophysitis.
- Discuss the epidemiology and pathophysiology of ICI-associated hypophysitis.
- Discuss outcomes and management of ICI-associated hypophysitis.

Significance of the Clinical Problem

ICIs have transformed the landscape of oncology. According to some estimates, approximately 56% of all patients with advanced cancer are eligible for ICI treatment.¹ Currently, 15 immune checkpoint inhibitors are approved by the US FDA in 4 categories:

1. Anticytotoxic T-lymphocyte antigen 4 (CTLA-4): ipilimumab, tremelimumab
2. Antiprogrammed cell death protein 1 (PD-1): nivolumab, pembrolizumab, cemiplimab, dostalimab, retifanlimab, toripalimab, tislelizumab, penpulimab
3. Antiprogrammed death-ligand 1 (PD-L1): atezolizumab, durvalumab, avelumab, cosibelimab

4. Antilymphocyte-activation gene 3 (LAG-3): relatlimab

Hypophysitis is a well-recognized adverse effect of these medications. The prevalence of ICI-associated hypophysitis varies by agent subclass. The risk is higher with regimens that include anti-CTLA-4 agents and may be elevated in combination therapy (anti-CTLA-4 + anti-PD-1; anti-PD-1 + anti-LAG-3) compared with either agent alone.²⁻⁸ Reported rates of ICI-associated hypophysitis also vary by study type (prospective oncologic studies vs retrospective endocrinology-focused analyses) due to deficiencies (imprecise and often overlapping categories) in the common terminology criteria for adverse events used in oncology studies.⁹ In brief, the risk of ICI-associated hypophysitis appears to be 1% or less for monotherapy with anti-PD-1 or anti-PD-L1 agents, approximately 10% for anti-CTLA-4 monotherapy, 8% for anti-PD-1 + anti-LAG-3 (based on 1 study), and possibly up to 10% to 20% in some reports for anti-CTLA-4 + anti-PD-1 therapy.

Although pituitary inflammation in ICI-treated patients is self-limited and nonrecurrent with rare exceptions, hypopituitarism persists to some degree in nearly all patients.¹⁰ Some patient groups treated with ICIs have achieved impressive long-term survival rates and require ongoing hormone replacement.¹¹

Practice Gaps

- Reliable pretreatment predictors for the development of ICI-associated hypophysitis are lacking.
- The clinical presentation of ICI-associated hypophysitis varies, partly related to the type of agent, and may include nonspecific symptoms and mild or absent radiographic findings. Clinical awareness and timely multidisciplinary care are important for optimal patient management.
- ICI-associated hypophysitis is a clinical entity distinct from primary hypophysitis. Available data on the management of ICI-associated hypophysitis are almost exclusively retrospective, limiting the development of treatment strategies and guidelines.

Discussion

Mechanism

Briefly, anti-CTLA-4 antibodies act early in the immune response to increase T-cell proliferation and activity. T-cell activation occurs following antigen presentation on the major histocompatibility complex (MHC) and binding to the T-cell receptor, along with costimulation via engagement of B7-1/B7-2 ligands with CD28. CTLA-4 competitively inhibits CD28 and generates an opposing signal to serve as a brake after immune response activation. Anti-PD-1 and anti-PD-L1 agents act more peripherally to inhibit the immune response. PD-1 is expressed by activated lymphocytes and monocytes. PD-L1 is expressed by antigen-presenting cells and multiple other cell types, including some tumor cells (to evade immune surveillance). PD-1:PD-L1 binding reduces immune effector-cell proliferation, cytokine secretion, and granular enzyme/perforin production. LAG-3 is expressed by activated T cells and binds MHC II to generate an inhibitory signal.¹²⁻¹⁴

Agents targeting PD-1, PD-L1, and LAG-3 are hypothesized to induce hypophysitis by enhancing latent pituitary autoimmunity.

Anti-CTLA-4 therapy appears to directly bind to and target anterior pituitary cells expressing CTLA-4, thereby activating antibody-dependent cell-mediated cytotoxicity (ADCC) and the classical complement pathway.^{15,16} Ipilimumab and tremelimumab are immunoglobulin G1- and immunoglobulin G2-based antibodies, respectively, which are able to participate in these processes. With the exception of penpulimab, anti-PD-1 agents are immunoglobulin G4 (IgG4)-based antibodies, which have a poor ability to bind complement and activate Fc receptor subtypes. The LAG-3 inhibitor relatlimab is also an IgG4-based antibody. Penpulimab and the PD-L1 inhibitors atezolizumab and durvalumab cannot effectively bind Fc receptors or complement due to modified Fc domains. Avelumab and cosibelimab can activate ADCC and complement. Although several studies have reported variable levels of PD-L1 expression in pituitary adenomas, examination of normal pituitary glands has not found any significant expression.¹⁷⁻²⁰ PD-1 mRNA expression has been demonstrated in homogenates of pituitary adenomas and normal pituitary glands, possibly due to infiltrating immune cells.^{21,22} Rare autopsy specimens from patients with hypophysitis after anti-CTLA-4 and anti-PD-1 treatment have exhibited features consistent with the mechanisms described.^{16,23}

Clinical experience with individuals harboring germline *CTLA-4* mutations provides further support for direct targeting of the anterior pituitary by anti-CTLA-4 agents. Most individuals with these mutations have been diagnosed with various autoimmune diseases similar to immune-related adverse events (irAE) occurring after treatment with ipilimumab and tremelimumab. Significantly, no case of hypophysitis or hypopituitarism was reported among 158 individuals with *CTLA-4* mutations.²⁴⁻²⁶ On a similar note, *CTLA-4* polymorphisms have been associated with Graves disease, autoimmune hypothyroidism, and type 1 diabetes mellitus but not primary hypophysitis. Rare germline *PD-1* and *PD-L1* mutations have been reported; these individuals have not been diagnosed with hypophysitis.^{27,28}

Additionally, rare cases of ectopic tumoral ACTH expression and associated anti-pro-opiomelanocortin antibodies have been reported in patients with ICI-associated hypophysitis, as well as a case of anti-pituitary-specific positive transcription factor 1 (PIT-1) hypophysitis (ectopic tumoral PIT-1 expression and circulating anti-PIT-1 antibody).²⁹⁻³¹

Clinical Presentation, Diagnosis, and Management

Mechanistic data provide some insights into the clinical phenotypes of patients with ICI-associated hypophysitis (*Table 1*). Unlike in primary hypophysitis, arginine vasopressin deficiency is extremely rare in ICI-associated hypophysitis. This is consistent with pathology specimens demonstrating sparing of the posterior pituitary.^{16,23} Patients with ICI-associated hypophysitis that develops after treatment with anti-CTLA-4 agents commonly present with deficiencies across multiple anterior pituitary axes. Monotherapy with anti-PD-1 or anti-PD-L1 medications and combination therapy with anti-PD-1 + anti-LAG-3 most often cause isolated central adrenal insufficiency. Although

multiple axes may be affected at diagnosis in individuals with anti-CTLA-4 hypophysitis, nonadrenal axes can recover in many patients. However, central adrenal insufficiency is nearly universally permanent in ICI-associated hypophysitis, regardless of the agent utilized.^{3,6,32-34} Notably, central adrenal insufficiency in patients with ICI-associated hypophysitis is typically biochemically severe.

The timeline for ICI-associated hypophysitis is consistent with proposed mechanisms. Hypophysitis following anti-CTLA-4 monotherapy generally develops within a relatively narrow timeframe, usually between 4 and 16 weeks after treatment initiation (*Figure 1, following page*). Hypophysitis following anti-PD-1, anti-PD-L1, or combined anti-PD-1 + anti-LAG-3 treatment occurs over a much broader timeframe. Combination treatment with anti-CTLA-4 + anti-PD-1 appears to be a hybrid, but more closely resembles the timeline with anti-CTLA-4 monotherapy.^{3,6,32-34}

Symptomatically, headache is a more common presenting symptom in patients with hypophysitis treated with anti-CTLA-4 regimens. Non-CTLA-4-associated hypophysitis more often presents

Table 1. Clinical Features of ICI-Associated Hypophysitis

Feature	Treatment		
	Anti-CTLA-4, anti-CTLA-4 + anti-PD-1	Anti-PD-1, anti-PD-L1	Anti-PD-1 + anti-LAG-3 ^a
Risk of hypophysitis	10%, up to 10%-20%	<1 %	8%
Onset after ICI initiation	Majority 4-16 weeks, 4-24 weeks	Broad range without a clear peak	Broad range
Pituitary enlargement	Majority	Minority	Minority
Headaches	Common	Infrequent	Infrequent
Arginine vasopressin deficiency	Very rare	Very rare	None
Anterior pituitary deficiencies at diagnosis	Multiple axes commonly affected	Isolated central AI	Isolated central AI
Anterior pituitary deficiencies at follow-up	Persistent central AI	Persistent central AI	Persistent central AI

Abbreviations: AI, adrenal insufficiency; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; LAG-3, lymphocyte-activation gene 3; PD-L1, programmed death-ligand 1. ^a Only one cohort has been published to date.

with constitutional symptoms such as fatigue, anorexia, and myalgias/arthralgias. Hyponatremia is present at diagnosis in a significant portion of patients with ICI-associated hypophysitis.^{3,6,32-34}

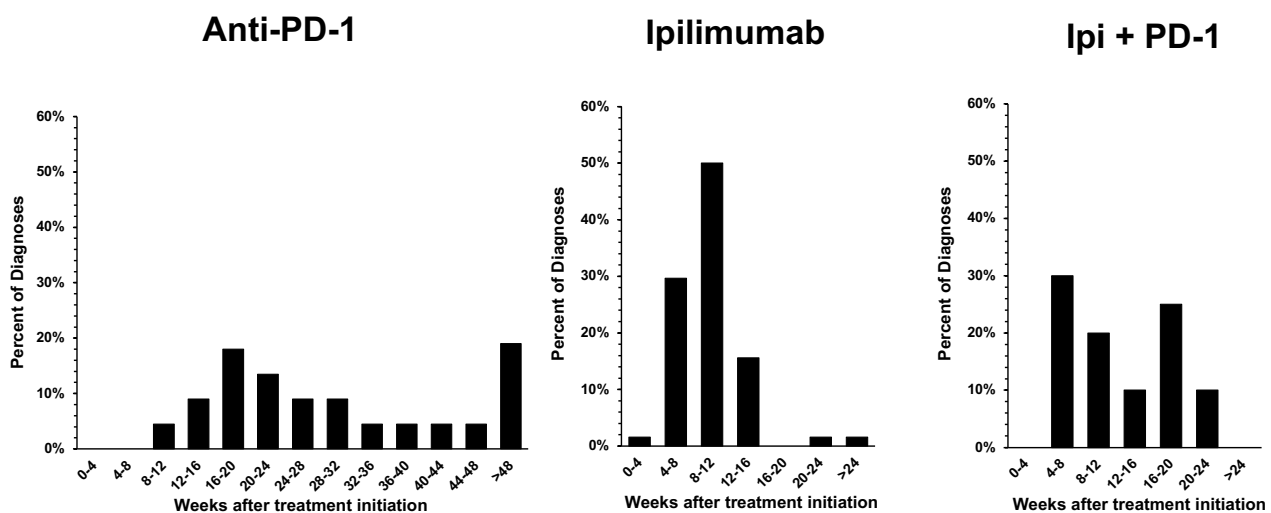
Radiographic changes are also more common in patients with ICI-associated hypophysitis after anti-CTLA-4 treatment. Pituitary gland enlargement is typically mild and may not be readily apparent without comparison to previous imaging. Optic nerve compression is very rare. Pituitary gland enhancement is often homogeneous but can sometimes be heterogeneous or even contain cystic elements. Stalk thickening may be present in some cases. Pituitary gland enlargement can precede symptom onset, is transient, and typically resolves within a couple of months. Subsequent pituitary gland atrophy occurs in some patients (*Figure 2, following page*). Rapid resolution and subtle initial radiographic findings may affect reported rates of radiographic findings in studies of ICI-associated hypophysitis.^{3,6,32-35} Other imaging modalities, such as PET, can complement MRI or serve as a useful diagnostic aid if MRI is unavailable.³⁶

Patients with primary hypophysitis are sometimes treated with pharmacologic dosages of glucocorticoids or other immunosuppressive medications, especially in the context of

uncontrolled headaches or cranial nerve deficits. Treatment of milder cases may sometimes be supportive. Optimal management strategies for primary hypophysitis are not well defined, and practice patterns vary. Published data on ICI-associated hypophysitis are likewise almost exclusively retrospective. Existing analyses have not shown a clear benefit of routine pharmacologic glucocorticoid use in ICI-associated hypophysitis. Pharmacologic glucocorticoids do not appear to yield clear benefits for symptom resolution, recovery of pituitary function, or speed of radiographic resolution.³⁷⁻³⁹ Nonetheless, pharmacologic glucocorticoids may be appropriate in rare cases of patients with recalcitrant severe headache or visual compromise.

Multiple studies suggest that the development of irAEs may correlate with improved treatment responses in patients receiving ICIs, although many of these studies lack landmark analyses to control for immortal time bias. Patients with severe irAEs treated with systemic glucocorticoids do not appear to have worse survival than patients not receiving such medications.^{40,41} Since severe irAEs may be associated with improved survival, they represent a potential confounding factor in these analyses. Little data exist comparing the effects on survival between immunosuppressive

Figure 1. Time to Hypophysitis Diagnosis After Initiation of ICI Therapy



Abbreviations: Ipi, ipilimumab; PD-1, programmed cell death protein 1. Reprinted from Faje A et al. *Eur J Endocrinol*, 2019; 181(3): 211-219. © European Society of Endocrinology. By permission of Oxford University Press.

and nonimmunosuppressive therapies for patients with the same irAE. Several studies have demonstrated that defects in the immune response can contribute to primary or acquired resistance to ICI therapy. High glucocorticoid dosages inhibit the immune response, including pathways linked to ICI resistance. Therefore, sufficient systemic glucocorticoid dosages over an adequate timeframe could be expected to affect the clinical antitumor efficacy of ICIs. Survival appeared to be improved in a retrospective analysis of patients with melanoma treated with lower glucocorticoid dosages for ICI-associated hypophysitis.³⁷ Given the lack of clear benefit from the routine use of pharmacologic glucocorticoids in patients with ICI-associated hypophysitis, the typically mild and self-limited nature of radiographic findings, and potential negative effects on antitumor treatment, management is generally supportive with physiologic dosages of glucocorticoids.

Recurrence of ICI-associated hypophysitis is extremely rare, and the diagnosis does not affect patient candidacy for future ICI therapy.

Reliable pretreatment predictors for ICI-associated hypophysitis have yet to be identified. The prevalence of preexisting autoimmune disease does not appear to be higher in patients treated with ICIs who develop hypophysitis compared with the general population.⁴² Several studies

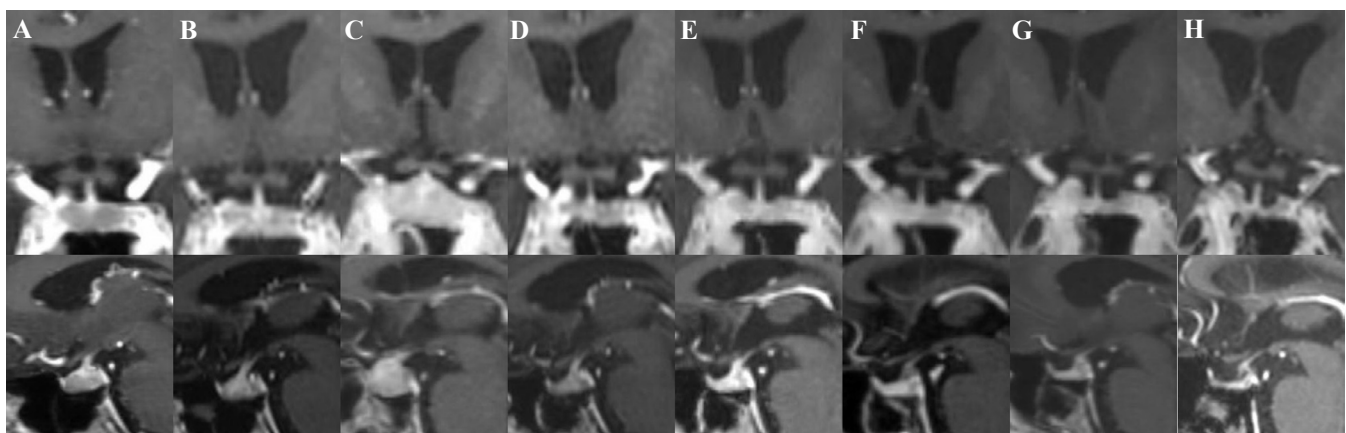
examining human leukocyte antigen subtypes in ICI-associated hypophysitis patients have yielded variable results. As previously noted, radiographic changes can precede symptom onset. A serial decline in TSH levels may also presage the development of hypophysitis in patients receiving anti-CTLA-4 regimens (when thyrotoxicosis is absent).^{35,43} Relative and absolute eosinophilia have also been described as potential predictors, although these findings are not specific to hypophysitis and can also occur with other irAEs.^{44,45} A small analysis suggested that a significant increase in serum antibody levels to guanine nucleotide-binding protein G subunit alpha and integral membrane protein 2B after initiation of ICI treatment predicted the development of hypophysitis.⁴⁶

Clinical Case Vignettes

Case 1

A 72-year-old man with a history of stage IV melanoma is treated with 2 cycles of ipilimumab + nivolumab. Three weeks after the second cycle, he develops severe fatigue, anorexia, and weight loss. He does not have headaches. ICI-associated hepatitis is diagnosed, and he is treated with prednisone (starting at 60 mg daily 2 months

Figure 2. MRI Changes in a Patient With Hypophysitis Secondary to Ipilimumab



Panel A, 2 days before ipilimumab initiation; Panel B, 4 days before diagnosis of hypophysitis; Panel C, Diagnosis of hypophysitis; Panel D, 4 days after diagnosis of hypophysitis; Panel E, 6 weeks after diagnosis; Panel F, 9 weeks after diagnosis; Panel G, 15 weeks after diagnosis; Panel H, 19 weeks after diagnosis. Reprinted from Chamorro-Pareja N et al. *Endocrinology*, 2024; 165(9): bqae084. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

after cycle 2 and tapered over 6 weeks) plus mycophenolate mofetil.

Laboratory testing is shown (Table 2).

MRI and FDG-PET are shown (Figure 3).

Which is the more likely diagnosis?

- A. Sellar metastasis
- B. ICI-associated hypophysitis

Answer: B) ICI-associated hypophysitis

The patient developed symptoms potentially consistent with adrenal insufficiency at a time point commonly associated with anti-CTLA-4 ICI regimens. Thyroid function tests showed declining TSH levels and transient central hypothyroidism (unlike adrenal insufficiency in ICI-associated hypophysitis, central hypothyroidism can be temporary). FDG-PET imaging showed sellar uptake, which can occur with hypophysitis (as well as pituitary adenomas, sellar metastases, and other tumoral or infiltrative processes). MRIs did not show a sellar mass or pituitary enlargement. This was not surprising. Pituitary enlargement can resolve rapidly in ICI-associated hypophysitis; the post-ICI treatment MRI was obtained a couple of months after symptom onset and abnormal laboratory testing. The patient developed recurrent severe fatigue after completion of the prednisone taper. Test results showed severe central adrenal insufficiency, which persisted on physiologic glucocorticoid replacement.

Case 2

A 53-year-old woman with stage IV breast cancer has been treated with pembrolizumab and eribulin for the past 4 months. She is admitted to the hospital with fatigue, failure to thrive, and low-grade fever. She does not have headaches. Her vital signs are stable. Laboratory testing shows undetectable cortisol levels following cosyntropin stimulation and an undetectable ACTH level. Serum sodium levels are normal, and

Figure 3. Case 1 MRIs and FDG-PET

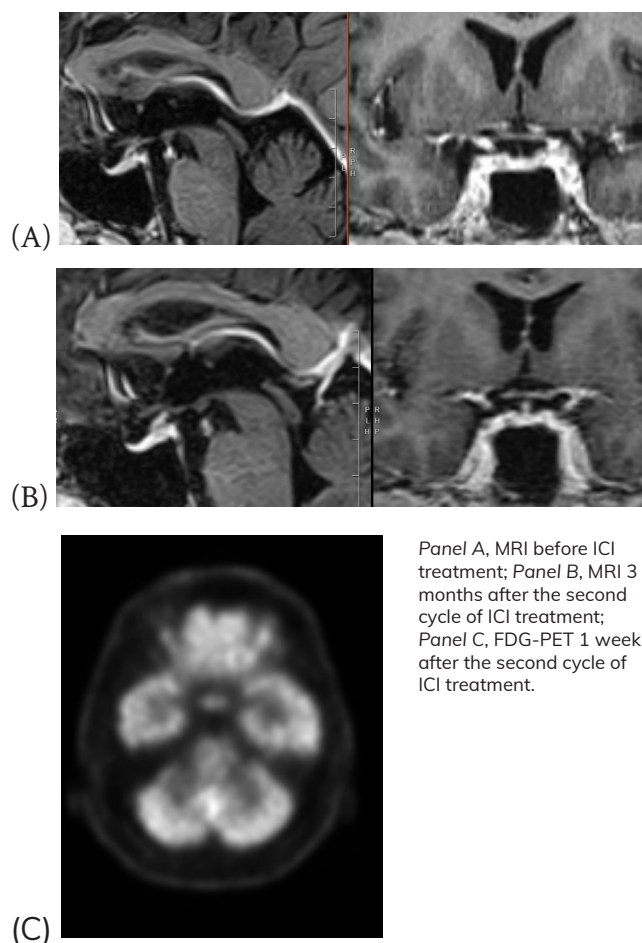


Table 2. Case 1 Patient's Laboratory Test Results

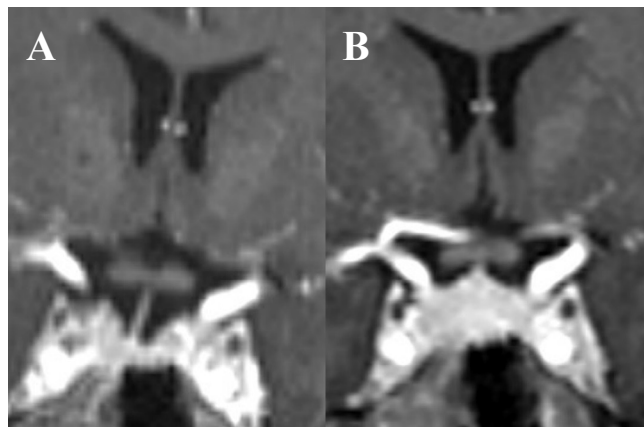
Analyte	At ICI initiation	Cycle 2	1 Month after cycle 2	2 Months after cycle 2
TSH	1.78 mIU/L	0.81 mIU/L	0.32 mIU/L	2.08 mIU/L
Free T ₄	1.1 ng/dL (SI: 14.2 pmol/L)	1.2 ng/dL (SI: 15.4 pmol/L)	0.6 ng/dL (SI: 7.7 pmol/L)	1.3 ng/dL (SI: 16.7 pmol/L)

Reference ranges: TSH, 0.40-5.00 mIU/L; free T₄, 0.9-1.8 ng/dL (SI: 11.6-23.2 pmol/L). Adapted from Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. Rasmussen KM & Yaktine AL, eds. Washington (DC): National Academies Press (US); 2009.

the remaining results of anterior pituitary function testing are normal. She does not have symptoms suggestive of arginine vasopressin deficiency.

MRIs are shown (*Figure 4*).

Figure 4. Case 2 MRIs



Panel A, MRI before ICI treatment; Panel B, MRI during hospital admission.

Which glucocorticoid dosage should the patient receive?

- A. Pharmacologic dosage
- B. Physiologic dosage

Answer: B) Physiologic dosage

MRI showed new diffuse pituitary gland enlargement with homogeneous enhancement, consistent with ICI-associated hypophysitis. The gland did not contact the optic apparatus. Testing showed isolated central adrenal insufficiency, which was consistent with her presenting symptoms and is the most common biochemical presentation in patients with ICI-associated hypophysitis treated with anti-PD-1 agents such as pembrolizumab. Studies have not demonstrated benefits from routine use of pharmacologic glucocorticoids for ICI-associated hypophysitis, although higher dosages may be reasonable in select cases with severe headache recalcitrant to other interventions or visual compromise. Some data suggest that higher glucocorticoid dosages may attenuate the antitumor efficacy of ICIs.

Case 3

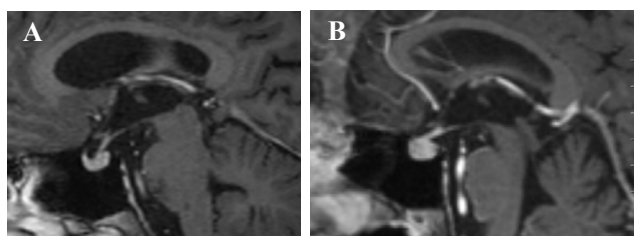
A 62-year-old man with a history of diabetes mellitus and stage IVD melanoma is treated with ipilimumab + nivolumab (4 cycles, completed 2 months prior to presentation) followed by nivolumab monotherapy, which is ongoing at the time of presentation. He feels well. On physical examination, vital signs are normal, and visual fields are full to confrontational testing.

Nonfasting laboratory test results (samples collected at 8:40 AM several days before presentation):

Sodium = 134 mEq/L (135-145 mEq/L)
(SI: 134 mmol/L [135-145 mmol/L])
Glucose = 241 mg/dL (SI: 13.3 mmol/L)
Hemoglobin, normal
Platelet count, normal
White blood cell count, normal
Eosinophils = 12.2% (<8%), 560/ μ L (<900/ μ L)
TSH = 0.36 mIU/L (0.40-5.00 mIU/L)
Free T₄ = 0.7 ng/dL (0.9-1.8 ng/dL) (SI: 9.0 pmol/L [11.6-23.2 pmol/L])
Cortisol = 15.0 μ g/dL (SI: 413.8 nmol/L)
ACTH = 55 pg/mL (6-76 pg/mL) (SI: 12.1 pmol/L [1.3-16.7 pmol/L])
Prolactin = 5.4 ng/mL (<15.2 ng/mL)
(SI: 0.23 nmol/L [<0.66 nmol/L])
Testosterone = 55 ng/dL (249-836 ng/dL)
(SI: 1.9 nmol/L [8.6-29.0 nmol/L])
LH = 1.6 mIU/mL (2.0-12.0 mIU/mL) (SI: 1.6 IU/L [2.0-12.0 IU/L])
FSH = 3.1 mIU/mL (1.0-12.0 mIU/mL) (SI: 3.1 IU/L [1.0-12.0 IU/L])
IGF-1 = 233 ng/mL (41-279 ng/mL) (SI: 30.5 nmol/L [5.4-36.5 nmol/L])

MRIs of the pituitary are shown (*Figure 5*).

Figure 5. Case 3 MRIs



Panel A, MRI before ICI treatment; Panel B, MRI at the time of presentation.

Which is the most appropriate next step in this patient's management?

- A. Start thyroid replacement
- B. Start thyroid and testosterone replacement
- C. Start glucocorticoid and thyroid replacement
- D. Do not start hormone replacement and monitor

Answer: C) Start glucocorticoid and thyroid replacement

The patient's clinical history, laboratory data, and radiographic imaging were consistent with ICI-associated hypophysitis. Although the patient did not have laboratory testing indicating the presence of cortisol deficiency, the development of permanent central adrenal insufficiency is nearly universal in such patients, and preemptive treatment with physiologic glucocorticoid replacement is reasonable. Other anterior pituitary hormone deficiencies may recover without intervention in some patients. Thyroid hormone replacement is a reasonable option, although observation could also be considered when mild central hypothyroidism is present. Subsequent

testing in this patient demonstrated persistent, severe central adrenal insufficiency and recovery of the thyroidal and gonadal axes.

Key Learning Points

- ICI-associated hypophysitis is a distinct entity from primary hypophysitis, and its clinical characteristics vary by ICI agent class.
- Permanent central adrenal insufficiency is nearly universal in patients with ICI-associated hypophysitis.
- Routine use of pharmacologic glucocorticoids for ICI-associated hypophysitis does not appear to be advantageous, and management is generally supportive with physiologic hormone replacement.
- ICI-associated hypophysitis is self-limited, essentially nonrecurrent, and does not impact candidacy for further ICI treatment.

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Current Approach to Acromegaly Care

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify the challenges in diagnosing acromegaly.
- Manage complex patients with acromegaly using multimodality therapy.
- Recommend the optimal approach for patients with acromegaly who want to become pregnant.

Significance of the Clinical Problem

Acromegaly is caused by GH excess, usually due to a GH-secreting pituitary adenoma. Given its rarity and the insidious nature of its presentation, the diagnosis often remains unrecognized for many years after initial symptoms.¹⁻⁵ Delayed diagnosis is associated with multiple comorbidities and more invasive disease, which makes surgical cure less likely.⁶ There have been advancements in medical therapies over the past 3 decades, including the use of dopamine agonists, somatostatin receptor ligands, and a GH receptor antagonist, and combined therapies have been used in patients who do not successfully respond to monotherapy.⁷ Outcomes using combination therapy have been successful in reported studies,⁷ but multidrug therapy for acromegaly is not FDA approved. In the last several years, newer oral somatostatin receptor ligand options have become available and

FDA approved for acromegaly, with efficacy and safety equivalent to that of injectable agents based on randomized prospective placebo-controlled trials.⁸⁻¹⁰ However, despite advances in surgical and medical therapies, improvement in time to diagnosis has been minimal.¹¹⁻¹³ Being diagnosed at a more advanced disease stage is associated with increased morbidity and mortality and decreased quality of life, and improving recognition of this disease at earlier stages is important.^{6,13}

Practice Gaps

- There is controversy about how to develop and implement universal strategies to predict which patients with acromegaly will respond to somatostatin receptor ligands.
- Data are limited on how to approach fertility and manage pregnancy in patients with acromegaly receiving medical therapy.
- There is an unmet need to diagnose acromegaly earlier and to raise awareness of the disease.

Discussion

A critical unmet need in acromegaly care is decreasing the time from the first signs and symptoms to diagnosis. Before 2000, the mean delay ranged from 6.6 years to more than 20 years¹⁻⁴ vs the mean time to diagnosis of 3.2 to 5.5 years after 2000.^{1-4,12} In the current era, strides have been made in medical and surgical therapies, but a significant delay remains with a median of

approximately 5 years to diagnose acromegaly and more than 10 years in a significant subset of patients,^{6,11,13} with limited progress over recent decades in diagnosing acromegaly earlier.¹² Later diagnosis is associated with increased morbidity and mortality.⁶ Diagnosis is delayed longer (by 2 years) for women than for men,^{12,13} highlighting the specific need to improve detection of acromegaly in women. The delay in diagnosing acromegaly exceeds that observed for Cushing disease, prolactinomas, and nonfunctioning pituitary adenomas.¹³

Possible strategies to enhance early diagnosis include universal screening, facial recognition software, and machine-learning programs based on hand photographs and voice recordings.¹⁴⁻¹⁹ However, these raise concerns about the cost-effectiveness of screening for rare diseases, the complex ethics of facial recognition, and the lack of ethnic heterogeneity, since the populations sampled in most studies were homogeneous and lacked a variety of ethnicities used to develop the software, all of which deter universal implementation.

Once acromegaly is recognized as a possible diagnosis, confirming it is straightforward. If classic clinical features of acromegaly are present, an elevated serum IGF-1 level is sufficient for diagnosis, but in equivocal cases, either because IGF-1 is only borderline-high or because clinical features are unclear, an oral glucose tolerance test should also be done to prove lack of suppression of GH to less than 1.0 ng/mL (<1.0 µg/L). In newer assays, a cutoff less than 0.4 ng/mL (<0.4 µg/L) has been proposed.²⁰

Given the diagnostic delay typically encountered in patients with acromegaly, most present with macroadenomas (adenomas ≥1 cm), and many have invasive disease, including invasion of the cavernous sinus, which makes complete resection with transsphenoidal surgery less likely. For patients not cured after surgery, several medical therapies are approved.⁷ The main first-line medical therapy is somatostatin receptor ligands, which not only have the potential to improve IGF-1 levels but also to control tumor growth in 50% to 60% of responsive patients. Lanreotide and octreotide are

long-acting injectable agents, typically administered monthly and mostly targeting somatostatin receptor 2 (SST2). Pasireotide binds preferentially to somatostatin receptor 5 (SST5), in addition to SST2, making it more effective for tumors with lower SST2 expression. New oral agents targeting SST2, such as oral octreotide and paltusotine, have been approved. These agents demonstrate efficacy equivalent to that of lanreotide and octreotide injectable agents in randomized controlled clinical trials⁷ and may appeal to patients who prefer daily oral pills to monthly injections. Pegvisomant, a GH receptor antagonist, should work in all patients to effectively normalize IGF-1 levels if taken correctly, as it blocks signaling at the level of the normal GH receptor (not directly at the tumor).^{21,22} Cabergoline, a commonly used oral dopamine receptor agonist, can be used to treat acromegaly in patients with mild disease or as add-on therapy in combination with other drugs. Neither combination therapy nor cabergoline has been specifically FDA approved for use in acromegaly.^{7,23,24}

Radiation therapy remains an option for patients not cured after surgery, particularly in patients who do not respond to, tolerate, or have access to medical therapies. A recent acromegaly Pituitary Society consensus summarizes a strategy with currently available treatments (*Figure 1, following page*).²³

Women with acromegaly who remain uncured after surgery and seek fertility pose a challenge because the safety of medical therapies for acromegaly during pregnancy has been minimally studied. Outcomes are generally favorable, partly because the high estrogen levels during pregnancy reduce IGF-1 levels, but little is known about the fetal effects of drugs used to treat acromegaly, and there are case reports of both fetal macrosomia and microsomia associated with the use of somatostatin receptor ligands during pregnancy.²⁵ However, uncontrolled acromegaly increases the risk of gestational diabetes, hypertension, and toxemia.^{25,26} The ideal strategy would be for patients to achieve IGF-1 and tumor control before conceiving and, if possible, to discontinue and wash out medical therapy before conception.

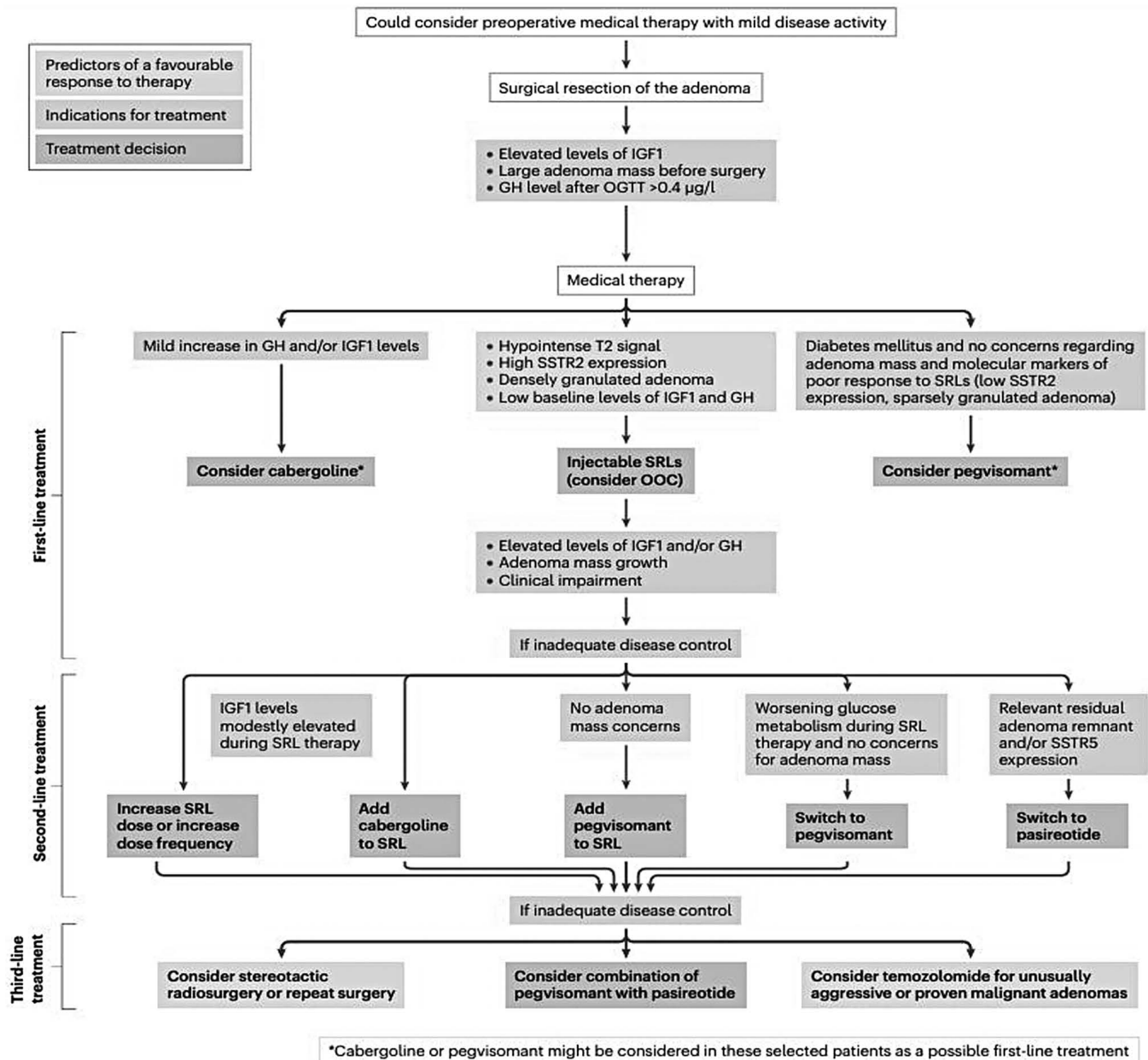
Clinical Case Vignettes

Case 1

A 45-year-old woman is referred to an endocrinologist for a high prolactin value. Her medical history includes sleep apnea diagnosed at age 35 years, prediabetes diagnosed at age 40 years, bilateral carpal tunnel syndrome diagnosed at age

41 years, and jaw malocclusion diagnosed at age 42 years. Medications include fluoxetine and inclisiran (PCSK9 inhibitor). She reports fatigue (since age 35), night sweats, joint pain, and increased saliva. Notes in her medical history state, “no features of Cushing,” and the suggestion to repeat prolactin measurement off fluoxetine and to perform MRI. Her prolactin concentration is slightly

Figure 1. Pituitary Society Acromegaly Consensus

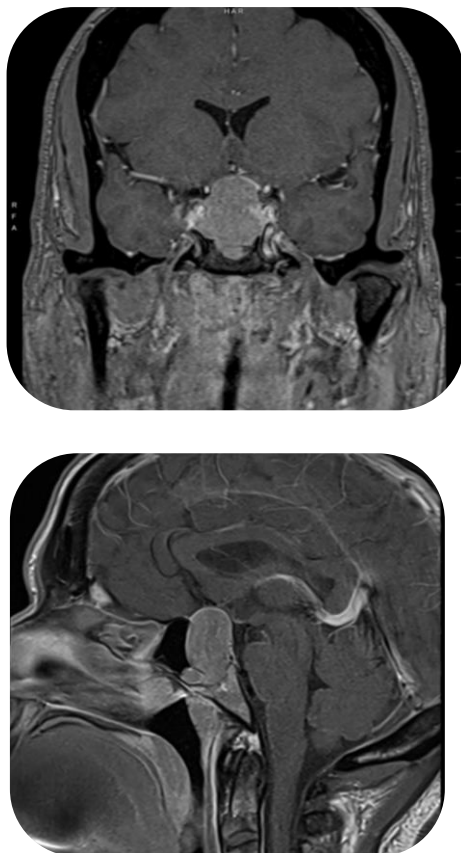


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high at 39 ng/mL (SI: 1.7 nmol/L) (reference range, 0-23 ng/mL [SI: 0-1.0 nmol/L]), and MRI shows a large macroadenoma with suprasellar extension (*Figure 2*). She is referred to a pituitary-focused neurosurgeon who recognizes facial features of acromegaly: enlarged lips and tongue, slight protrusion of the lower jaw, and widened nasal bridge.

Figure 2. Case 1 Patient MRI



Laboratory test results:

IGF-1 = 578 ng/dL (30-317 ng/dL) (SI: 75.7 nmol/L [3.9-41.5 nmol/L])

Random GH = 47 ng/mL (<7 ng/mL) (SI: 47 µg/L [<7 µg/L])

Which of the following therapies would be best for this patient?

- Transsphenoidal resection by an expert pituitary neurosurgeon
- Craniotomy by a skull-based expert neurosurgeon
- Primary medical therapy given that the invasive tumor is unlikely to be completely resected
- Transsphenoidal surgery followed by radiation to prevent a recurrence
- Dopamine agonist, given the high prolactin, and monitoring of IGF-1 and performing MRI

Answer: A) Transsphenoidal resection by an expert pituitary neurosurgeon

Transsphenoidal resection by an expert pituitary neurosurgeon (Answer A) is the best first-line therapy for a possible cure, provided there are no contraindications to surgery and an expert pituitary surgeon is available.

A craniotomy performed by a skull-based expert (Answer B) would not be the first approach and carries a higher risk of complications. Debulking with transsphenoidal surgery would be the safer first-line approach.

Even if this patient is not surgically cured, she is more likely to have a better response to medical therapy with somatostatin receptor ligands after debulking. Thus, primary medical therapy (Answer C) is not the best initial approach.

Transsphenoidal surgery followed by radiation to prevent a recurrence (Answer D) is wrong because she may not need radiotherapy if cured by surgery, or if she is responsive to medical therapy after surgery, even if not cured.

Starting a dopamine agonist, given the high prolactin value, and monitoring IGF-1 and performing MRI (Answer E) is not advised because her IGF-1 level is higher than that expected to be controlled with a dopamine agonist, making it unlikely to sufficiently reduce her tumor.

Case 1, Continued

Her history of sleep apnea, prediabetes, bilateral carpal tunnel syndrome, and jaw malocclusion was most likely due to which of the following?

- A. High prolactin
- B. Autoimmune disease
- C. Obesity
- D. Acromegaly (not yet diagnosed)
- E. Polycystic ovary syndrome

Answer: D) Acromegaly (not yet diagnosed)

In this case, many subspecialists failed to piece together the clues over decades, resulting in the delayed diagnosis of acromegaly (Answer D).

High prolactin levels (Answer A) (hyperprolactinemia or prolactinoma) are less likely to be associated with sleep apnea, carpal tunnel syndrome, and jaw malocclusion.

Autoimmune disease (Answer B) typically would not cause this constellation of findings, particularly sleep apnea.

Obesity (Answer C) and polycystic ovary syndrome (Answer E) may be associated with prediabetes and sleep apnea but are less likely to also cause carpal tunnel and jaw malocclusion.

Case 2

An 18-year-old man presents for evaluation of hypogonadism and headaches. He notes fatigue and depression that started 9 months ago. He has had no changes in ring or shoe size, changes in jaw size, or new spaces between his teeth.

On physical examination, he is tall with no obvious signs of acromegaly except for mild coarsening and thickening of his brow and nasal bridge. His blood pressure and heart rate are normal. His height is 76 in (193 cm), and weight is 225 lb (102 kg).

Laboratory test results:

IGF-1 = 869 ng/mL (108-548 ng/mL)
(SI: 113.8 nmol/L [14.2-71.8 nmol/L])
Random GH = 19 ng/mL (SI: 19 µg/L)

Testosterone = 115 ng/dL (50-1100 ng/dL)
(SI: 3.9 nmol/L [1.7-38.2 nmol/L])

Cortisol, normal

Cosyntropin-stimulation test, normal

Free T₄, normal

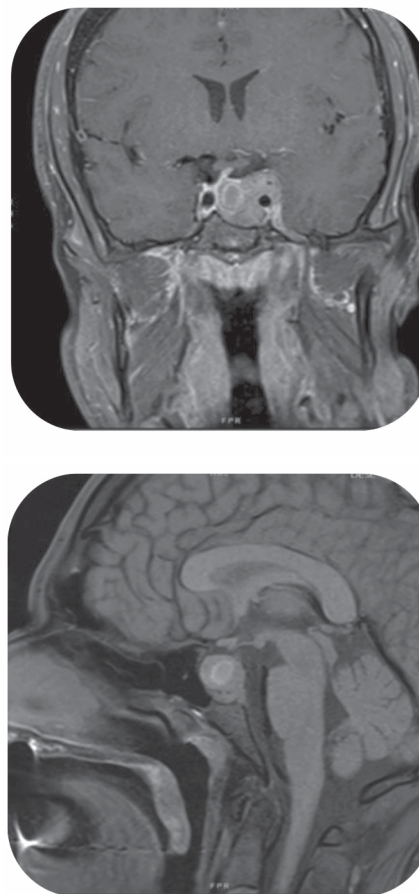
TSH, normal

Hemoglobin A_{1c} = 5.5% (37 mmol/mol)

Prolactin (in dilution) = 954 ng/mL (2-18 ng/mL)
(SI: 41.48 nmol/L [0.09-0.78 nmol/L])

Pituitary MRI shows a 3 × 2 × 2-cm macroadenoma extending into the left cavernous sinus without suprasellar extension and a normal optic chiasm (Figure 3).

Figure 3. Case 2 Patient MRIs at Diagnosis



Which of the following is the best initial therapeutic approach?

- A. Since he is young, avoid any invasive procedures until after genetic testing is completed
- B. Cabergoline because his prolactin is elevated
- C. Radiation therapy because it is unlikely that the cavernous sinus lesion can be fully resected
- D. Surgical therapy with an experienced pituitary surgeon
- E. Reassure him that GH levels can be elevated in adolescents and young adults who are still growing

Answer: D) Surgical therapy with an experienced pituitary surgeon

Since this patient is young, genetic testing is indicated, but treatment should not be delayed while awaiting the results (Answer A).

Although his prolactin is elevated and cabergoline (Answer B) may be suitable medical therapy at some point, cabergoline would likely be inadequate to control his high IGF-1 level.

Surgery (Answer D) could potentially provide a cure; if not curative, debulking would increase the likelihood of a favorable response to a somatostatin receptor ligand, with normalization of IGF-1.

Radiation (Answer C) should be reserved as a last resort in this young man, particularly given normal hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes.

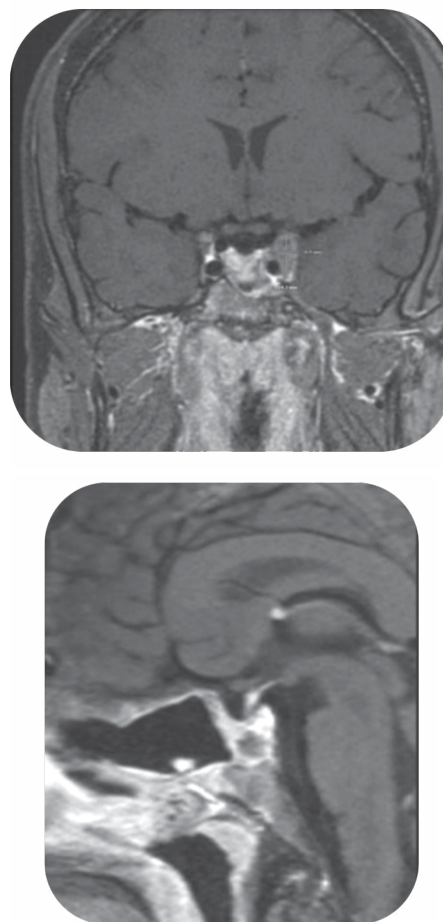
GH may be high in adolescents (Answer E), but his IGF-1 value is well above the normal range for his age, and MRI shows an invasive macroadenoma consistent with acromegaly, which warrants therapy.

Case 2, Continued

He undergoes transsphenoidal surgery with an experienced pituitary surgeon and has no complications. Pathology shows a mixed prolactin- and somatotropin-secreting adenoma that is Pit-1 positive. However, postoperatively, his IGF-1

concentration remains elevated at 711 ng/mL (93.1 nmol/L), and a small amount of residual tumor in the left cavernous sinus is observed on MRI (Figure 4).

Figure 4. Case 2 Patient MRI After Transsphenoidal Surgery



Which of the following is the best next step for this patient now?

- A. Craniotomy
- B. Radiation therapy
- C. Medical therapy with a somatostatin receptor ligand
- D. Medical therapy with a GH receptor antagonist
- E. Medical therapy and radiation therapy

Answer: C) Medical therapy with a somatostatin receptor ligand

A craniotomy (Answer A) should be avoided if medical therapy can be effective because it has an increased risk of neurosurgical complications and could cause permanent neurologic or pituitary deficits.

Radiation (Answer B) should only be considered if medical therapy fails or if he cannot tolerate it, as it may cause long-term, permanent hypopituitarism and, less commonly, neurocognitive or neurologic complications.

There is a low risk associated with a trial of a somatostatin receptor ligand (Answer C); if he responds, it may normalize IGF-1 levels and shrink the tumor.

Medical therapy with the GH receptor antagonist pegvisomant (Answer D) is an option, either as monotherapy or as an add-on to somatostatin receptor ligand therapy, if the patient does not respond to somatostatin receptor ligand therapy alone. However, pegvisomant is unlikely to reduce tumor size, and because a tumor remnant remains, somatostatin receptor ligand therapy would be a better option for suppressing tumor growth.

Ultimately, medical therapy and radiation therapy (Answer E) may be needed if the tumor grows or medical therapy does not normalize IGF-1 and symptoms, but radiation therapy should not be used until the response to medical therapy is determined.

Case 3

A 33-year-old woman with a history of acromegaly wishes to conceive. She was treated with transsphenoidal surgery and radiation therapy and is currently receiving medical therapy to control GH excess. She presented at age 30 years with bilateral visual field defects and noted an increase in the size of her hands and feet, difficulty biting down, headaches, sweating, and snoring. She also reported irregular menstrual cycles that were treated with an oral contraceptive pill.

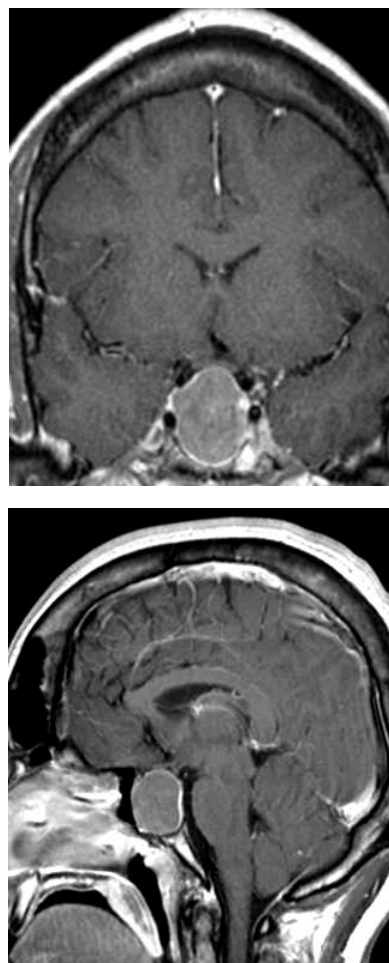
Physical examination revealed broadening of her nose, widening of her forehead, thickening of her lips, coarsened facial features, spaces between her teeth, macroglossia, thickening of her fingers, doughy hands, and multiple skin tags on her face and her back.

Laboratory test results baseline at diagnosis before surgery:

IGF-1 = 900 ng/mL (53-351 ng/mL)
(SI: 117.9 nmol/L [6.9-46.0 nmol/L])
Random GH = 56 ng/mL (<7 ng/mL) (SI: 56 µg/L
[<7 µg/L])
Prolactin = 57 ng/mL (0.1-23.3 ng/mL)
(SI: 2.48 nmol/L [0-1.01 nmol/L])

Other hormonal function testing before surgery included normal free T₄ measurement, TSH measurement, and cosyntropin-stimulation testing. Her hypothalamic-pituitary-gonadal axis could not be reliably assessed because she was on an oral contraceptive pill. Pituitary MRI showed a large, invasive macroadenoma extending into the left cavernous sinus and some suprasellar extension with compression of the optic chiasm (Figure 5).

Figure 5. Case 3 Patient MRI



Which of the following would you have advised at the time of her initial presentation before surgery?

- A. Confirm with an oral glucose tolerance test before therapeutic intervention
- B. Recommend radiation therapy
- C. Suggest primary medical therapy with cabergoline
- D. Refer to an experienced pituitary surgeon
- E. Begin pegvisomant

Answer: D) Refer to an experienced pituitary surgeon

This patient should have been referred to an experienced pituitary surgeon (Answer D) for primary therapy with transsphenoidal surgery. Surgery was indicated to relieve optic chiasm compression and prevent further vision loss. Primary medical therapy with cabergoline (Answer C) would not have been the best option.

Since this was a clear case of acromegaly based on her classic clinical features and her definitive evidence of GH excess on laboratory testing, oral glucose tolerance testing (Answer A) was unnecessary.

Radiation (Answer B) may have been necessary if other therapies failed, but it would not have been recommended as first-line therapy.

Ultimately, she may require pegvisomant (Answer E) to control and/or normalize IGF-1, but the first step was to reduce the tumor size through surgical resection.

Case 3, Continued

After transsphenoidal surgery, pathology reveals some GH staining and a sparsely granulated somatotroph adenoma, with an elevated Ki-67 proliferation index of 4%. Six weeks after surgery, MRI shows partial resection of the large macroadenoma. Visual fields have normalized, but a residual lesion remains in the left cavernous sinus.

Finding which transcription factor would confirm a somatotroph adenoma?

- A. Pit-1
- B. T-Pit
- C. SF-1
- D. Transcription factors associated with GH-secreting adenomas have not yet been identified
- E. Both Pit-1 and T-Pit

Answer: A) Pit-1

Pit-1 (Answer A) is the transcription factor associated with GH-secreting adenomas. Prolactinomas also demonstrate Pit-1 staining. T-Pit (Answer B) is diagnostic of a corticotrophic adenoma, while SF-1 (Answer C) is diagnostic of a gonadotroph adenoma. Answer D is incorrect because Pit-1 is associated with GH-secreting adenomas.

Case 3, Continued

She is receiving medical therapy, but IGF-1 levels have not normalized despite the maximum dosage of a somatostatin receptor ligand (lanreotide LAR, 120 mg monthly). Pegvisomant, 30 mg daily, is added. With combination therapy, she achieves biochemical control, with IGF-1 levels normalizing (237 ng/mL [31.0 nmol/L]). She continues taking an oral contraceptive pill, as she has been advised to avoid pregnancy during her treatment for acromegaly. She expresses a desire to conceive as soon as it is safe to do so.

Given her goal, which of the following is the best advice?

- A. Stop the oral contraceptive pill and try to conceive now while well-controlled on medical therapy
- B. Switch to cabergoline and stop birth control and other medications, and suggest she try to conceive immediately before biochemical control is lost

- C. Recommend radiation therapy, and once the tumor is stable and IGF-1 has improved or is stable, switch to cabergoline and/or short-acting octreotide, and withdraw and washout octreotide LAR for several months before conception
- D. Refer to the in vitro fertilization team and let them advise on the management of medical therapy for acromegaly before conception
- E. Given high risk, avoid pregnancy and consider surrogacy or adoption

Answer: C) Recommend radiation therapy, and once the tumor is stable and IGF-1 has improved or is stable, switch to cabergoline and/or short-acting octreotide, and withdraw and washout octreotide LAR for several months before conception

Once radiated (Answer C), this tumor is unlikely to grow. More than 90% of pituitary adenomas do not grow after radiation; thus, tumor growth during pregnancy would be less of a concern. She is on a long-acting somatostatin receptor ligand, which will take at least 3 months to wash out. Therefore, Answers A and B are wrong because they do not allow time for the washout of the somatostatin receptor ligand, which could affect the fetus.

Answer D is incorrect because, although referring for in vitro fertilization for fertility is acceptable, it is the endocrinologist's responsibility to manage acromegaly before conception. The reproductive endocrine team will likely rely on the endocrine expert for guidance or may lack knowledge of the medical therapy for acromegaly and its importance before fertility treatment.

Answer E is wrong because patients with acromegaly have successful pregnancy outcomes for both mother and fetus in most cases. Even in a patient with severe disease, pregnancy is not contraindicated, provided appropriate precautions are taken.

Key Learning Points

- Several comorbidities may cluster but not be recognized as indications for evaluating for acromegaly. These include sleep apnea, carpal tunnel syndrome, hypertension, prediabetes or diabetes, joint abnormalities, a history of joint replacements, and gonadal dysfunction.
- Acromegaly is diagnosed by documenting an elevated serum IGF-1 level in a patient with suggestive signs or symptoms, usually accompanied by a visible adenoma on imaging. Because the signs and symptoms develop slowly over time and due to the rarity of this diagnosis, it is often unrecognized until late in the presentation, when treatment becomes more difficult, achieving a surgical cure is more challenging, and there is an increase in comorbidities and mortality.
- Goals of therapy include normalizing IGF-1 levels and controlling tumor growth. Surgery remains the first-line management in most cases.
- Medical therapy for acromegaly includes dopamine agonists, somatostatin receptor ligands, and GH receptor antagonists. Primary medical therapy may be used for invasive tumors, which are unlikely to be completely resected, if chiasmal compression is not present. Radiation therapy, stereotactic or fractionated, is used for uncontrolled tumors or high GH/IGF-1 and if medications fail, are not tolerated, or are unavailable to the patient.
- Patients with acromegaly can conceive and have successful pregnancy outcomes. Ideally, IGF-1 levels and tumor growth should be controlled before pregnancy. If possible, it is ideal to wash out medical therapy with somatostatin receptor ligands or pegvisomant before conception.
- During pregnancy, patients with acromegaly should be carefully monitored for the development of gestational diabetes and hypertension, and those with residual tumor should have their visual fields assessed every trimester.

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Management of Pituitary Apoplexy

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify the main clinical manifestations of pituitary apoplexy and the imaging findings associated with this condition.
- Guide the immediate management of pituitary apoplexy.
- Describe the outcomes of conservative and surgical management of pituitary apoplexy.

Significance of the Clinical Problem

Pituitary apoplexy is a rare clinical syndrome caused by acute hemorrhage and/or infarction in the pituitary gland. It most commonly presents in the context of an undiagnosed pituitary tumor. Based on epidemiological studies, the incidence of pituitary apoplexy is 0.17 episodes per 100,000¹ and the prevalence is 6.2 cases per 100,000.² In a cohort of conservatively managed nonfunctioning pituitary macroadenomas, the incidence was 0.30 per 100 patient-years (95%

CI, 0.18-0.49).³ Pituitary apoplexy occurs more frequently in the fifth or sixth decade of life, has a male preponderance, and is more common in nonfunctioning pituitary adenomas. Although it can occur in microadenomas, most cases involve adenomas larger than 1 cm. Several precipitating factors have been reported (eg, major surgery, invasive procedures, medications such as dopamine agonists, GnRH analogues, anticoagulants or antithrombotic drugs, dynamic endocrine testing, head trauma), although causation for all these factors has not been proven.⁴

The presenting manifestations of pituitary apoplexy vary with the extent of hemorrhage, necrosis, and edema.⁵ An acute, severe headache is the most common symptom, mimicking other acute neurological events. Other manifestations include nausea and vomiting, visual impairment from distention of the optic chiasm or optic nerves caused by the bulging sellar mass, and ocular nerve palsies (cranial nerves III, IV, and VI) from sudden extension into the cavernous sinus. Among the oculomotor nerves, cranial nerve III is most often affected, leading to ptosis, limited adduction, and mydriasis. Visual field defects are reported in 36% to 71% of affected individuals, with a rapid decrease in visual acuity in 39% to 56%.⁴ Photophobia, meningismus, and sometimes

fever can also occur. Impaired consciousness is a sign of severity. Compression of the carotid artery or cerebral vasospasm can cause cerebral ischemia and neurological manifestations, such as hemiparesis, dysphasia, or a pyramidal syndrome.⁵ Pituitary hormone deficits can also occur, attributed to damage to the anterior pituitary or increased pressure on the stalk, disrupting the release of hypothalamic and/or pituitary hormones.⁵ ACTH deficiency has been reported in 70% to 76% of affected individuals and can result in hemodynamic instability, hyponatremia, and adrenal crisis.⁴ Other causes of hyponatremia in the setting of pituitary apoplexy include syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, and nausea/vomiting. TSH and gonadotropin deficiencies have been reported in 50% to 57% and 76% to 79%, respectively, whereas arginine vasopressin (AVP) deficiency is rare at presentation (0% to 8%).⁴

Although not always pathognomonic, imaging is paramount for the timely diagnosis of apoplexy. Characteristic imaging features reflect the underlying pathophysiological process in pituitary apoplexy, which includes simple infarction with little or no hemorrhagic component, hemorrhagic infarction, mixed hemorrhagic infarction and clot, or pure clot.⁵ CT is the initial radiologic modality performed at presentation and is also used to exclude subarachnoid hemorrhage. On CT, a recent hemorrhage appears as a hyperdense lesion with minimal contrast enhancement; over time, it becomes progressively less hyperdense, making it more difficult to differentiate from other intrapituitary lesions (eg, cysts).⁴ Conventional MRI sequences (T1W/T2W) may not show an infarct for 6 hours, and small infarcts may be difficult to detect on CT for days. For these reasons, diffusion-weighted imaging (DWI) can be informative early in the apoplexy process, demonstrating increased DWI signal in ischemic tissue within minutes after arterial occlusion and increased signal intensity relative to normal gray and white matter in ischemic apoplexy.⁵ In the first hours after the onset of apoplexy, typical hyperintensity on T1W sequences may not be

present, either due to infarction or because the hemorrhage is in the form of deoxyhemoglobin.⁵ After this interval, acute hemorrhagic apoplexy appears hyperintense or isointense on T1W images (due to the transformation from deoxyhemoglobin to methemoglobin) and hypointense on T2W images. Later (after about 7 days), the hemorrhagic area becomes hyperintense on both T1W and T2W images, whereas in the chronic phase (after about 2 weeks), a heterogeneous appearance is usually present.⁴ The differential diagnosis includes subarachnoid hemorrhage, bacterial meningitis, ophthalmoplegic migraine, suprasellar aneurysm, stroke, hypertensive encephalopathy, and cavernous sinus thrombosis.⁴

Practice Gaps

- Predictors of visual outcomes and the extent or severity of visual compromise that dictate surgical intervention need to be elucidated.
- The optimal timing of surgical intervention relative to the onset of pituitary apoplexy remains unclear.
- Prospective and, if feasible, randomized trials, as well as carefully validated tools to guide optimal management of pituitary apoplexy, are required.
- Patient outcomes from large-scale studies are needed, with particular focus on the risk of pituitary tumor regrowth during long-term follow-up.

Discussion

Immediate Management When Pituitary Apoplexy Is Suspected

When pituitary apoplexy is suspected, immediate action is required. This includes supportive measures to maintain hemodynamic stability (eg, fluid resuscitation, administration of stress-dose glucocorticoids); assessment and management of fluid and electrolyte balance; urgent biochemical

and hormonal assessment (including full blood cell count, liver and kidney function tests, coagulation screening, and pituitary function); visual assessment (either bedside or formal); and urgent imaging (brain CT, MRI). In adults, proposed glucocorticoid regimens are hydrocortisone, 100 mg intramuscular bolus, followed by 50 to 100 mg intramuscular injections every 6 hours, or 100 to 200 mg intravenous bolus, followed by a continuous intravenous infusion of 2 to 4 mg per hour.⁶ Oral glucocorticoids in the initial acute phase are not advised because nausea and vomiting may be present. Later, as the patient recovers, hydrocortisone should be tapered to a maintenance oral dosage of 20 to 30 mg daily, usually in 3 divided doses. High-dosage dexamethasone instead of stress-dose hydrocortisone has been used in the acute phase of pituitary apoplexy, especially when an antioedematous effect is sought.^{7,8} Randomized controlled trials comparing the effectiveness of various glucocorticoids administered during the acute phase of pituitary apoplexy for long-term visual, endocrine, and radiological outcomes are lacking. Therefore, it is not possible to determine the superiority of any glucocorticoid over the others. After the initial urgent evaluation of cranial nerve function and visual fields to confrontation, a formal visual assessment (including Humphrey testing or Goldmann perimetry) should be performed once the patient is clinically stable, preferably within 24 hours of suspected diagnosis.⁹ Continuous monitoring of vital signs, neurological and visual status, blood pressure, fluid balance, and blood electrolytes is crucial, especially given the risk of sudden deterioration. In severe cases, this monitoring should take place in intensive care units. Daily ophthalmologic review, formal visual field testing, and acuity assessments are necessary and will help guide management decisions. If there is deterioration in clinical status, visual acuity, visual fields, or level of consciousness, urgent MRI should be arranged, and immediate decompression surgery should be considered.⁴

Overall, the care of patients with pituitary apoplexy in the acute phase requires a multidisciplinary approach and close collaboration

among endocrinology, pituitary surgery, ophthalmology, and radiology teams.

Surgical and Conservative Management

Indications for surgical management of pituitary apoplexy include severe impairment or deterioration of visual acuity, visual fields, or consciousness. Partial or complete resolution of visual field defects and visual acuity has been reported in 5% to 57% and 6% to 57% of cases, respectively, and complete resolution of oculomotor nerve palsies in 63% to 83% during variable follow-up periods.^{4,7,10-13} Improvement in visual function occurs immediately after surgery and lasts for varying periods.¹⁴ Notably, because the optic nerve has a low tolerance for ischemia, both severe impairment and a long delay until treatment are important predictors of poor recovery of vision.¹⁴ There is no consensus on how the timing of surgery (immediate or delayed) affects visual function recovery.^{15,16} Some degree of hypopituitarism persists in 43% to 87% of patients, and permanent AVP deficiency has been reported in 2% to 14.8%.^{4,8}

When conservative management is chosen, careful monitoring is essential to detect any deterioration in the clinical course that would necessitate surgical intervention. Conservative management can also be considered for frail patients who are poor surgical candidates. Partial or complete resolution of visual field defects and visual acuity has been reported in 25% to 80% and 12% to 75% of patients, respectively, and complete resolution of oculomotor nerve palsies in 75% to 100% of patients during variable follow-up periods.^{4,7,10-13} Various pituitary hormone deficits have been reported in 31.5% to 83% of patients,^{8,10-12} and marked tumor shrinkage has been observed in more than half during follow-up.^{4,16} Most functioning pituitary tumors remain active after apoplexy, although spontaneous biochemical remission has also been reported.^{4,7}

Determining which management approach yields the best long-term outcomes is challenging

because of selection bias in choosing the management strategy, as patients who are most severely affected are usually directed toward surgery. A recent prospective, multicenter, observational, nonrandomized study suggested that conservative and surgical management yielded similar 3-month outcomes.¹⁶ Currently, the available literature suggests that patients with a mild clinical picture, without severe, progressive neuro-ophthalmic signs, can be safely managed conservatively.

In all cases, long-term follow-up is essential to optimize pituitary hormone replacement, detect potential hyperfunctionality of the pituitary tumor, and monitor tumor progression or regrowth.

Clinical Case Vignettes

Case 1

A 65-year-old man presents to the emergency department with an intense headache of sudden onset and acute deterioration of temporal visual fields. He has a history of atrial fibrillation and is taking apixaban. There is a suspicion of pituitary apoplexy, but he has no history of a pituitary tumor.

Which of the following is correct?

- A. Pituitary apoplexy is very unlikely because he has no history of a pituitary tumor
- B. Brain CT should be the first imaging modality
- C. In pituitary apoplexy, cranial nerve IV is the most frequently affected oculomotor nerve
- D. In the very first hours after the onset of apoplexy, typical hyperintensity on T1W MRI sequences is always present
- E. AVP deficiency is not a manifestation of pituitary apoplexy at presentation

Answer: B) Brain CT should be the first imaging modality

Brain CT (Answer B) is mandatory to exclude subarachnoid hemorrhage and to identify a sellar mass.

In most cases of pituitary apoplexy, there is no known history of a pituitary tumor (Answer A).

Among the oculomotor nerves, cranial nerve III is the most frequently affected (Answer C).

MRI may not be helpful in the first few hours after the onset of apoplexy, and the diagnosis may be missed. This is because the typical hyperintensity on T1W MRI sequences may be absent (Answer D), either due to infarction or deoxyhemoglobin.

Although rare, AVP deficiency may occur in pituitary apoplexy (Answer E), and assessment of fluid balance is necessary.

Case 1, Continued

Regarding the immediate management of pituitary apoplexy in this patient, which of the following is correct?

- A. Glucocorticoids should be offered after ACTH deficiency is confirmed
- B. In the acute phase of pituitary apoplexy, oral glucocorticoids are preferred over parenteral ones
- C. High-dosage dexamethasone is the most effective glucocorticoid regimen
- D. Immediate actions should include measures to maintain hemodynamic stability, assess and manage fluid and electrolyte balance, perform urgent biochemical and hormonal assessments, conduct visual assessment, and obtain urgent imaging
- E. Sudden deterioration in clinical status during the first days of apoplexy is not expected

Answer: D) Immediate actions should include measures to maintain hemodynamic stability, assess and manage fluid and electrolyte balance, perform urgent biochemical and hormonal assessments, conduct visual assessment, and obtain urgent imaging

Immediate actions should include measures to maintain hemodynamic stability, assess and manage fluid and electrolyte balance, perform urgent biochemical and hormonal assessments, conduct visual assessment, and obtain urgent imaging (Answer D).

Stress-dose glucocorticoids are recommended as soon as there is clinical suspicion of pituitary apoplexy, even before the results of the ACTH axis are available (Answer A).

In the acute phase of pituitary apoplexy, with nausea and vomiting potentially present, oral administration of glucocorticoids is not advised (Answer B).

There are no randomized controlled trials establishing the superiority of dexamethasone administration in the acute phase of pituitary apoplexy (Answer C).

Sudden deterioration in clinical status during the first days of apoplexy is possible, and close monitoring is needed during hospitalization (Answer E).

Case 2

Which of the following statements regarding the management of pituitary apoplexy is correct?

- A. Patients who have experienced pituitary apoplexy can recover pituitary function during follow-up
- B. Marked pituitary tumor shrinkage occurs in 15% of patients after conservative management of pituitary apoplexy
- C. Spontaneous biochemical remission of functioning pituitary tumors that developed apoplexy is not possible
- D. Oculomotor nerve palsies recover in less than 20% of patients after conservative management of pituitary apoplexy
- E. Permanent AVP deficiency occurs in 25% of patients after surgical management of pituitary apoplexy

Answer: A) Patients who have experienced pituitary apoplexy can recover pituitary function during follow-up

Patients who have experienced pituitary apoplexy can recover pituitary function during follow-up (Answer A), and recovery rates vary across published series.

Marked pituitary tumor shrinkage is observed in more than half of patients with pituitary apoplexy managed conservatively (Answer B).

Spontaneous biochemical remission of a functioning pituitary tumor after an apoplectic event is rare but still possible (Answer C).

Oculomotor nerve palsies typically recover after conservative management of pituitary apoplexy (Answer D).

Permanent AVP deficiency after surgical management of pituitary apoplexy occurs in 2% to 14.8% of patients (Answer E).

Key Learning Points

- Pituitary apoplexy is a medical emergency, and maintaining a high index of suspicion is essential for prompt diagnosis and management.
- The care of patients with pituitary apoplexy in the acute phase requires a multidisciplinary approach and close collaboration among the endocrinology, pituitary surgery, ophthalmology, and radiology teams.
- The decision between conservative and surgical management is individualized, with visual dysfunction and level of consciousness serving as the primary criteria for selecting the appropriate approach.
- Regular long-term follow-up is essential to optimize pituitary hormone replacement and monitor tumor progression and regrowth.

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Diagnosis and Management of Silent Pheochromocytoma and Paraganglioma

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the pathways of catecholamine synthesis, storage, secretion, and metabolism.
- Explain and accurately use consistent terminology for the different types of “silent” pheochromocytoma and paraganglioma (PPGL).
- Evaluate available strategies for managing patients with silent PPGL.

Significance of the Clinical Problem

PPGLs are rare neuroendocrine neoplasms arising from the chromaffin cells of the adrenal medulla or extra-adrenal paraganglionic tissue. Their clinical presentation primarily depends on their ability to synthesize and secrete catecholamines. When present, signs and symptoms are highly heterogeneous and often nonspecific. Thus, diagnosis relies mainly on the measurement of plasma free or urinary metanephrines, the O-methylated metabolites of catecholamines.¹

Over the past decades, the term “silent” PPGL has been increasingly used to describe tumors that do not produce the typical signs and symptoms of catecholamine excess.² This trend is largely attributable to the widespread use of anatomic

imaging and the expansion of surveillance and follow-up programs for individuals with genetic predisposition or a history of PPGL, respectively. In such cases, tumors are often detected at an early stage of development, when still too small to generate overt clinical manifestations of catecholamine excess. Alongside the term “silent” PPGL, alternative terms such as “nonsecretory,” “biochemically silent,” and “nonfunctional” PPGL have been increasingly and inconsistently used, often without clear distinction regarding the actual capacity of these tumors to synthesize or secrete catecholamines. To address the need for a unified and meaningful terminology, standardized definitions have recently been introduced based on: (a) the presence or absence of clinical manifestations of apparent catecholamine excess, (b) the tumor’s capacity to release catecholamines (nonsecretory), (c) the presence of positive or negative biochemical signal (biochemically negative), and finally (d) the tumor’s ability to synthesize catecholamines (nonfunctional).³

Practice Gaps

- Before defining a PPGL as clinically silent, a thorough clinical history is essential. In particular, most clinicians primarily focus their interest on the presence or absence of paroxysmal hypertension. However, this feature has repeatedly been shown to have limited utility for stratifying patients according to their true likelihood of disease. Other

manifestations, such as palpitations, tremor, pallor, nausea, low BMI, or tachycardia, are often discounted by physicians despite their high diagnostic value.

- Clinicians often use the terms “nonsecretory,” “biochemically negative,” and “nonfunctional” interchangeably, despite their distinct meanings. “Nonsecretory” tumors have very low secretory activity but are functional PPGLs, with dense intratumoral vesicular storage of epinephrine and norepinephrine, resulting in large amounts of tumor catecholamines.
- The term “biochemically silent” is often used to describe tumors with negative biochemical test results, although in many cases this reflects false-negative results due to inappropriate selection of biochemical markers, suboptimal assay methodology, or unsuitable reference ranges.
- Truly nonfunctional tumors cannot synthesize or secrete catecholamines, and definitive assessment of tumor functionality can only be established by direct measurement of catecholamines in tumor tissue. This term is most commonly applied to the head and neck paragangliomas (HNPGs), most of which do not produce catecholamines.
- According to international guidelines, the definitive treatment of functional PPGL is surgical resection, preceded by appropriate preoperative pharmacological blockade to reduce the risk of perioperative cardiovascular complications. In contrast, management of nonfunctional tumors is primarily determined by their site of origin. Although surgery remains the treatment of choice for rare nonfunctional, abdominal paragangliomas, the indication for surgical intervention in nonfunctional HNPGs depends primarily on tumor location, multifocality, patient age, and the presence or absence of pathogenic variants (PVs) in *SDHx* genes.

Discussion

Genetics

As more genetic causes of PPGL have been identified over the past 20 years, the prevalence of germline PVs in tumor susceptibility genes has increased to 40% in adults and up to 80% in children with PPGLs.⁴ These susceptibility genes can be classified into 2 main clinically relevant cluster groups. Cluster 1 PPGLs are characterized by activation of the hypoxia signaling pathways and include those associated with PVs in the von Hippel-Lindau (*VHL*) suppressor gene, the 4 subunits of the succinate dehydrogenase complex (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), the enzyme responsible for flavination of the *SDHA* subunit (*SDHAF2*), fumarate hydratase, malate dehydrogenase 2, and prolyl hydroxylases 1 and 2. Cluster 2 PPGLs are characterized by activation of kinase receptor signaling pathways. This cluster includes the neurofibromatosis type 1 (*NF1*) tumor suppressor gene, the rearranged during transfection (*RET*) proto-oncogene, the transmembrane protein 127 (*TMEM127*) gene, and the MYC-associated factor X (*MAX*) gene.

Pathways of Catecholamine Synthesis, Storage, Secretion, and Metabolism

Before defining a PPGL as “silent,” it is essential to review the pathways involved in catecholamine synthesis, storage, metabolism, and secretion. Catecholamine biosynthesis begins with the conversion of tyrosine to L-dihydroxyphenylalanine (L-DOPA), catalyzed by tyrosine hydroxylase, the rate-limiting enzyme in catecholamine production. L-DOPA is subsequently converted to dopamine by aromatic L-amino acid decarboxylase. Dopamine is transported into secretory vesicles, where it is converted to norepinephrine by dopamine β -hydroxylase. In adrenal chromaffin cells, norepinephrine is further converted to epinephrine by the cytoplasmic enzyme phenylethanolamine N-methyltransferase

(PNMT). Catecholamines are actively secreted from chromaffin cells primarily through an exocytotic process, which may occur either episodically or at low rates. In addition to their secretion, catecholamines continuously leak from storage vesicles into the cytoplasm.⁵ The presence of catechol-O-methyltransferase (COMT) within the cytoplasm facilitates the conversion of norepinephrine to normetanephrine and epinephrine to metanephrine. These O-methylated metabolites then passively diffuse from chromaffin cells into the circulation (*Figure 1*).

Approximately half of all adrenal paragangliomas produce both epinephrine and norepinephrine, whereas most of the remaining PPGLs predominantly or exclusively secrete norepinephrine (noradrenergic tumors).⁶ These biochemical differences reflect the capacity of the chromaffin cell to express PNMT, the enzyme responsible for converting norepinephrine to epinephrine. In contrast, PPGLs exhibiting minimal or absent expression of dopamine β -hydroxylase, the enzyme that converts dopamine to norepinephrine, may produce and secrete combinations of dopamine and norepinephrine,

or in some cases only dopamine. Such tumors are classified as noradrenergic/dopaminergic PPGLs.⁷⁻⁹

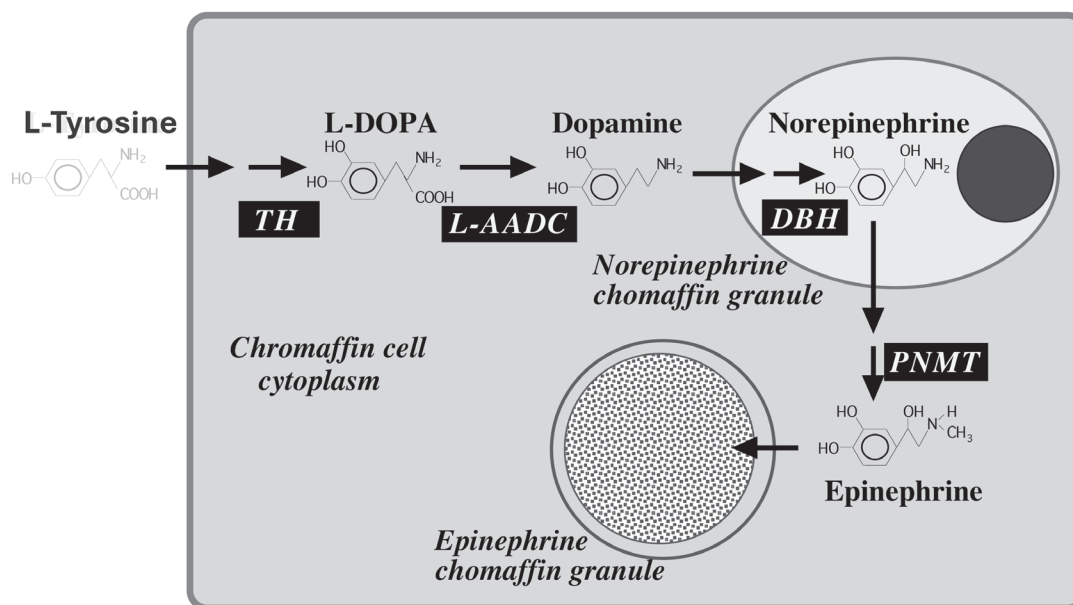
Silent PPGL

Over the past decades, the term “silent” PPGL has been increasingly used without a clear or consistent relationship to the clinical and biochemical presentation of affected patients. To facilitate precise scientific communication and ensure consistent interpretation, standardized definitions for the various forms of the “silent PPGL” have been proposed.³

Clinically Silent PPGL

Several factors may contribute to the absence of overt clinical manifestations in PPGL, including small tumor size, low catecholamine secretion, adrenoreceptor desensitization, and compensatory physiological responses. Indeed, PPGLs are slow-growing tumors that often take many years to reach a clinically relevant size.¹⁰ Thus, tumors detected at an early stage of development, such as incidental masses found during imaging studies performed for unrelated reasons, or masses detected during surveillance programs of patients with hereditary risk or history of PPGL, are

Figure 1. Pathways of Catecholamine Synthesis and Storage



[Color—Print (Color Gallery page CG17) or web & ePub editions]

frequently asymptomatic at diagnosis. Beyond tumor size, clinical expression is influenced by the type and pattern of catecholamine secretion and the magnitude of adaptive responses. In particular, epinephrine exerts stronger β_1 - and β_2 -adrenoreceptor activity than norepinephrine, leading to increased cardiac output and greater systolic blood pressure responses. Consequently, noradrenergic PPGLs are more often normotensive and clinically silent than adrenergic (eg, multiple endocrine neoplasia type 2 PPGLs). Moreover, noradrenergic PPGLs typically secrete catecholamines in a sustained manner, which may lead to tachyphylaxis, especially at older ages. In addition, noradrenergic PPGLs have sparse secretory stores, which may further limit their clinical expression. Finally, many PPGLs are classified as clinically silent due to incomplete clinical evaluation. Physicians concentrate their interest mainly on the presence or absence of hypertension, whereas symptoms such as hyperhidrosis, palpitations, tremor, pallor, nausea, and low BMI are frequently discounted despite their high diagnostic relevance.¹¹ A thorough clinical history is, therefore, essential before defining a PPGL as clinically silent.

Nonsecretory PPGL

The term nonsecretory PPGL should be reserved for tumors that consistently demonstrate an absence of catecholamine secretion, as confirmed by repeated measurements of plasma or 24-hour urinary catecholamine excretion. Nonsecretory PPGLs are most commonly adrenergic tumors, including those associated with PVs in cluster 2 genes. As previously noted, catecholamines are actively secreted from chromaffin cells or tumors primarily via exocytosis, a process that can occur episodically or at low rates. Cluster 2 adrenergic PPGLs display very low secretory activity, with daily secretion that often accounts for less than 5% of total catecholamine content. Consequently, such neoplasms may present with consistently normal plasma concentrations or urinary excretion of norepinephrine and epinephrine.¹² Regardless of their secretion, catecholamines continuously

leak from the dense storage vesicles of cluster 2 adrenergic PPGLs into the cytoplasm, where they are converted to metanephrines by the enzyme COMT.⁷ The metanephrines then passively diffuse from chromaffin cells into the circulation, thereby providing a reliable biochemical signal with elevations of plasma free or urinary metanephrines despite normal catecholamine concentrations.¹³

Biochemically Negative PPGL

Patients with PPGL and negative biochemical test results are often described as having “biochemically silent” tumors. However, in many cases, negative findings reflect false-negative results due to inappropriate biomarker selection, analytical methods, or reference intervals.^{14,15} Therefore, the term biochemically negative is now considered more accurate than biochemically silent. Metanephrines are the most sensitive and specific biochemical markers for PPGL because they are produced continuously and independently of catecholamine secretion within chromaffin cells by COMT, and they are not generated in sympathetic nerves. Importantly, plasma free metanephrines demonstrate superior diagnostic performance compared with urinary free or fractionated metabolites, particularly in patients at high risk.¹⁶ Inclusion of plasma methoxytyramine in the plasma panel further enhances the detection of the rather rare dopamine-producing tumors, including some HNPGLs. Accurate diagnosis of PPGL additionally depends on the use of appropriate analytical methods. Mass spectrometric-based methods offer higher sensitivity than immunoassays, which are associated with substantial rates of false-negative results.¹⁷ Finally, biochemical test interpretation must rely on appropriate reference ranges, including age-adjusted upper cutoffs for normetanephrine in adults and age- and sex-specific cutoffs for children and adolescents, as indicated in international guidelines.

Although most reported cases of biochemically negative PPGL reflect false-negative biochemical testing, a small subset represents truly biochemically negative neoplasms.^{18,19} These cases most

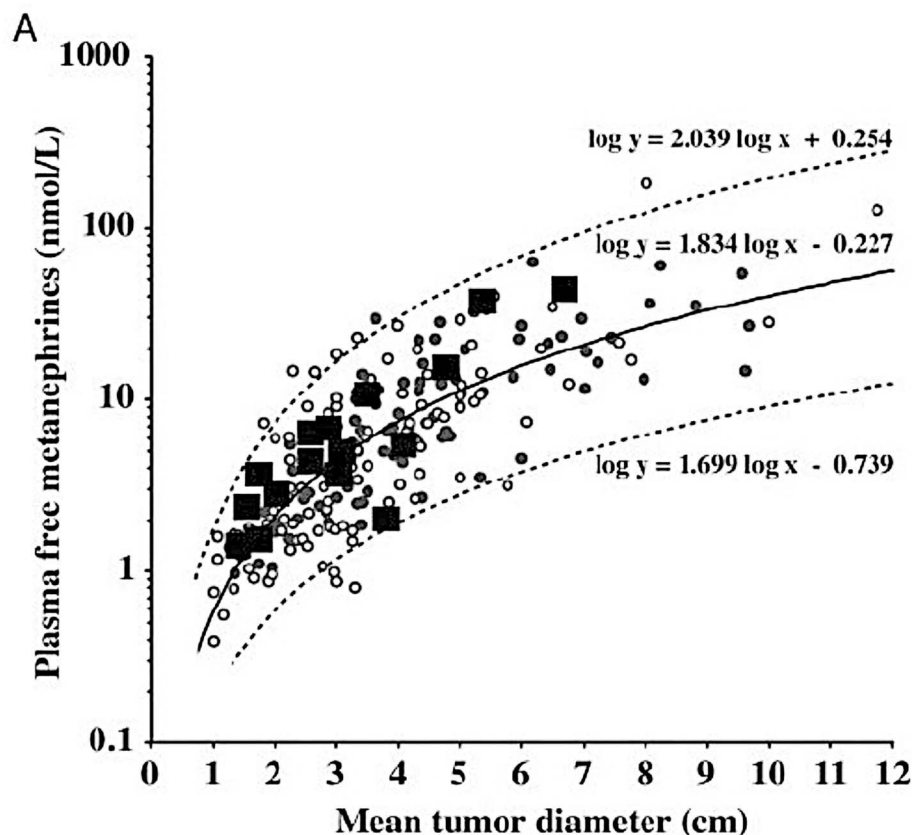
commonly involve functional PPGL at an early stage of development, when lesions are still too small (typically <1 cm) to generate a significant biochemical signal. Such small, biochemically negative PPGLs are frequently identified during surveillance programs in patients with PVs in tumor susceptibility genes or during follow-up of patients with a history of PPGL. In addition, early-stage PPGL may be discovered incidentally on imaging studies performed for unrelated clinical reasons.

Nonfunctional PPGL

Nonfunctional PPGLs do not produce or release catecholamines. In most cases, this absence of catecholamine output reflects a defect in catecholamine biosynthesis, typically due to a lack of tyrosine hydroxylase, the rate-limiting enzyme in this pathway. Most nonfunctional PPGLs occur in the head and neck region (HNPPGL) and typically do not synthesize catecholamines.

However, up to one-third of HNPPGLs generate small amounts of dopamine.²⁰ In such instances, these tumors are considered functional, as the presence of tyrosine hydroxylase enables dopamine production directly within the cytoplasm of chromaffin cells, even in the absence of secretory granules. However, nonfunctional abdominal PPGLs are extremely rare and frequently associated with PVs in the *SDHB* gene.²¹ These tumors often reach a substantial size before detection, likely due to the absence of relevant signs and symptoms, and they are more often linked to an immature phenotype and a higher risk of metastasis. The definitive confirmation of lack of functionality relies on biochemical analysis of tumor tissue catecholamines, as well as assessment of tyrosine hydroxylase expression. Preoperatively, nonfunctional PPGLs may be suspected when tumor size is not positively correlated with the sum of plasma normetanephrine and

Figure 2. Relationship Between Tumor Size and the Sum of Plasma Free Normetanephrine and Metanephrine



Adapted from Eisenhofer G et al. *Clinical Chemistry*, 2005; 51(4): 735–744. Copyright © The American Association for Clinical Chemistry.

metanephrine concentrations (*Figure 2*). This relationship, which can only be evaluated using plasma rather than urinary metanephrines, helps differentiate nonfunctional PPGL from small PPGLs that are simply biochemically negative.

Management of Silent PPGL

Preoperative Pharmacological Preparation of Silent PPGL

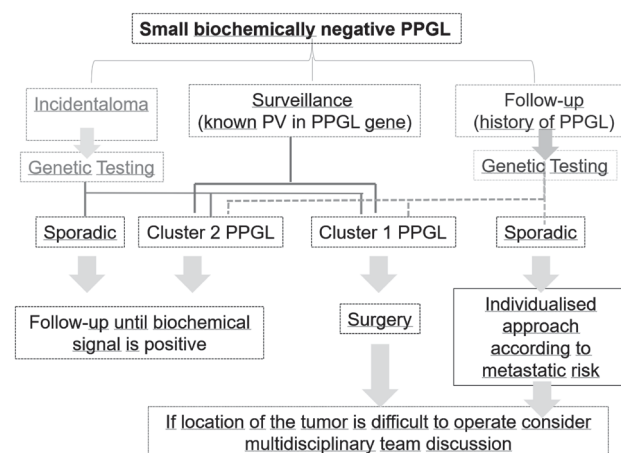
Both clinically silent and nonsecretory PPGL are classified as functional tumors because they retain the capacity to synthesize and store catecholamines. Consequently, these tumors may exhibit detectable elevations in plasma free or urinary metanephrines despite the absence of overt clinical symptoms or having normal circulating catecholamines. Similar to other functional PPGLs, they carry a significant risk of abrupt catecholamine release during surgical manipulation, which can precipitate severe intraoperative hemodynamic instability. For this reason, current endocrine guidelines advocate preoperative pharmacological preparation, most commonly with α -adrenergic blockade or, when appropriate, with calcium-channel blockers, for all functional PPGLs.^{14,15} This recommendation extends to small, biochemically negative but functional PPGLs, which, despite the lack of sufficient biochemical signal, remain capable of catecholamine release during surgery and may therefore provoke hazardous hypertensive crises. In contrast, biochemically negative HNPGLs and rare large abdominal nonfunctional PPGLs, in which tumor size does not correlate with the sum of plasma free normetanephrine and metanephrine, may be regarded as nonfunctional. In such cases, routine preoperative pharmacological preparation is generally not required.

Management of Silent PPGL

Surgical resection remains the definitive treatment for all PPGLs. However, the management of small, biochemically negative but functional tumors, as determined preoperatively by the positive relationship between the sum of plasma free metanephrines and tumor size, can be individualized. Genetic testing plays a central

role in this process. For patients with small incidentalomas and negative genetic testing, or with PVs in cluster 2 susceptibility genes, with a low metastatic risk, active surveillance may be a reasonable approach until biochemical tests become positive, especially if this decision aligns with the patient's wishes and preferences. In contrast, patients carrying PVs in cluster 1 genes are at higher risk for metastasis, and early surgical intervention is generally preferred. However, when small PPGLs are located in anatomically challenging regions with higher surgical morbidity, decisions should be made within a multidisciplinary team to balance risks and benefits (*Figure 3*).

Figure 3. Workflow for the Management of Patients With Small Biochemically Negative PPGL



[Color—Print (Color Gallery page CG17) or web & ePub editions]

Rare abdominal nonfunctional PPGLs do not require preoperative α -adrenergic blockade. However, these patients should undergo surgery promptly, as these tumors are often biologically aggressive and associated with a high metastatic risk. Importantly, preoperative functional imaging to assess for metastatic disease is generally recommended in such cases, whereas biopsy is allowed if clinically indicated. Management of nonfunctional HNPGL is even more challenging.²² In patients with *SDHx* PVs, or unknown genetic status, preoperative functional imaging is essential to exclude the presence of additional sympathetic PPGLs that may be too small to produce a

positive biochemical signal. Any sympathetic PPGL identified in this context should ideally be managed before treating HNPGL. For large HNPGLs (>2 cm) and/or young patients, radical treatment of HNPGL is usually favored due to the higher risk of metastatic progression. For patients with HNPGL and negative genetic testing, the likelihood of having a synchronous (or metachronous) sympathetic PPGL is extremely low, and functional imaging to detect additional sympathetic tumors is generally not required to assess metastatic risk. Within this group, carotid body tumors warrant particular attention, and radical treatment is often advised due to the higher metastatic potential. In patients with other HNPGL subtypes, management decisions should primarily consider local symptoms, multifocality, radiologic features suggestive of malignancy, and patient-specific factors, and are best discussed within a multidisciplinary team (Figure 4).

Clinical Case Vignettes

Case 1

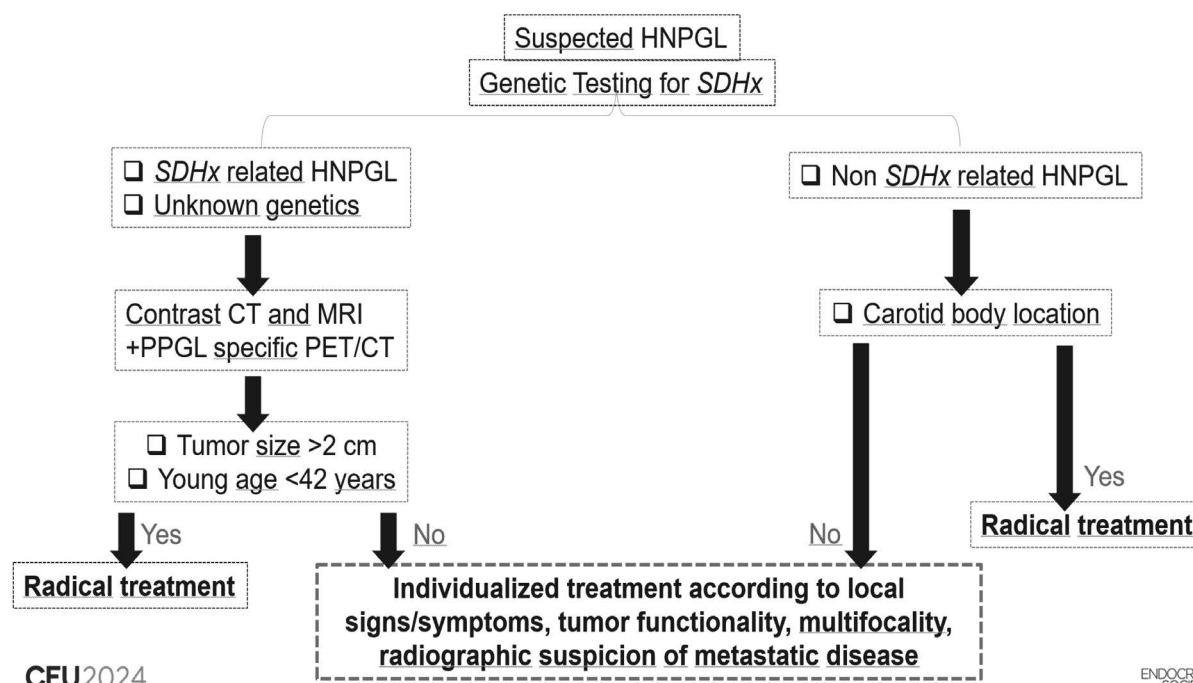
A 70-year-old woman with no history of hypertension or signs and symptoms potentially related to catecholamine excess is diagnosed with a 1.9 × 2.4-cm adrenal incidentaloma (Hounsfield units [HU] > 35), typical of PPGL. Biochemical workup reveals elevated plasma free normetanephrine, 2.5-fold above the age-adjusted upper cutoff, with normal plasma free metanephrine and methoxytyramine levels. Metanephrines are measured after 20 minutes of supine rest using liquid chromatography–tandem mass spectrometry, with age-adjusted reference ranges.

Which of the following best characterizes this patient's diagnosis?

- A. Clinically silent, functional PPGL
- B. Clinically silent, nonsecretory PPGL
- C. Clinically silent, nonfunctional PPGL
- D. No PPGL

Answer: A) Clinically silent, functional PPGL

Figure 4. Workflow for Managing Patients With Nonfunctional HNPGL



[Color—Print (Color Gallery page CG18) or web & ePub editions]

The patient exhibited no clinical signs or symptoms suggestive of catecholamine excess. Thus, the PPGL can be characterized as clinically silent. However, biochemical evaluation demonstrated elevated plasma free normetanephrine levels, confirming that the PPGL is functionally active. Metanephrines are continuously produced within chromaffin or tumor cells through intracytoplasmic metabolism of their parent catecholamines, independent of episodic catecholamine release. Plasma free metanephrines were measured under appropriate preanalytical and analytical conditions, making a false-positive elevation of plasma free normetanephrine unlikely.

Case 2

A 52-year-old woman is evaluated in the endocrinology outpatient clinic for paroxysmal hypertension, as well as hyperhidrosis and hot flashes during these episodes. Abdominal ultrasonography reveals a 2.5×2 -cm adrenal lesion (HU = 40), typical of PPGL. Biochemical workup reveals normal plasma norepinephrine and epinephrine in different sampling points, but isolated elevations in plasma free metanephrine levels. Metanephrines are measured after 20 minutes of supine rest, using liquid chromatography–tandem mass spectrometry, with age-adjusted reference ranges.

Which of the following best characterizes this patient's diagnosis?

- A. Secretory, functional PPGL
- B. Secretory, nonfunctional PPGL
- C. Nonsecretory, functional PPGL
- D. Nonsecretory, nonfunctional PPGL

Answer: C) Nonsecretory, functional PPGL

This represents an adrenergic PPGL characterized by isolated elevations of plasma free metanephrines. Most adrenergic PPGLs are nonsecretory because they exhibit very low secretory activity. Indeed, daily catecholamine release often accounts for less than 5% of the

total intratumoral catecholamine content. Consequently, plasma concentrations or urinary excretion of norepinephrine and epinephrine may remain within normal limits. Despite their low secretory output, these PPGLs are functionally active. They contain substantial intratumoral stores of catecholamines that continuously leak from dense-core storage vesicles into the cytoplasm, where COMT metabolizes them into metanephrines. These metanephrines then passively diffuse from chromaffin cells into the circulation, serving as a sensitive and reliable biochemical signal, namely, elevated plasma free or urinary metanephrines, even when circulating catecholamine concentrations are normal.

Case 3

A 55-year-old woman presents for evaluation of nonspecific loin pain and a 13.2-lb (6-kg) weight loss during the last 6 months. CT of the abdomen reveals a 5.4×4 -cm adrenal lesion, typical of PPGL. Biochemical workup reveals normal concentrations of plasma free normetanephrine, metanephrine, and methoxytyramine. Metanephrines are measured after 20 minutes of supine rest using liquid chromatography–tandem mass spectrometry, with age-adjusted reference ranges.

Which of the following best characterizes this patient's diagnosis?

- A. Biochemically negative, functional PPGL
- B. Nonsecretory, functional PPGL
- C. Biochemically negative, nonfunctional PPGL
- D. Secretory, functional PPGL

Answer: C) Biochemically negative, nonfunctional PPGL

This case represents a biochemically negative, nonfunctional abdominal PPGL. Such nonfunctional abdominal PPGLs are exceptionally rare and are frequently associated with PVs in the *SDHB* gene. They often attain considerable size before detection, most likely due to the absence of clinically relevant catecholamine-related signs and symptoms. To definitively confirm

nonfunctionality, biochemical quantification of intratumoral catecholamines and assessment of tyrosine hydroxylase expression within tumor tissue are necessary. However, preoperatively, nonfunctionality may be suspected when there is no positive correlation between tumor size and the combined plasma concentrations of normetanephrine and metanephrine.

Key Learning Points

- “Silent” PPGL is not a single entity. The terms clinically silent, nonsecretory, biochemically negative, and nonfunctional describe distinct biological and clinical states. Precise terminology is essential because each category has different diagnostic and therapeutic implications.
- A thorough clinical history is mandatory before labeling a tumor as clinically silent. Hypertension alone has limited value in assessing the likelihood of a PPGL. Symptoms such as palpitations, tremor, pallor, hyperhidrosis, nausea, tachycardia, and low BMI are frequently underrecognized but diagnostically important. Thus, a thorough clinical history is mandatory before labeling a tumor as clinically silent.
- Plasma free metanephrines are the most sensitive biochemical markers. Metanephrines are continuously produced within chromaffin cells via COMT, independent of episodic catecholamine secretion, and provide superior diagnostic accuracy compared with their parent catecholamines. Plasma free metanephrines also demonstrate slightly better diagnostic performance compared to 24-hour urinary (free or fractionated) metanephrines, particularly in patients at high risk for PPGL. Use of liquid chromatography–tandem mass spectrometry and appropriate age-adjusted reference ranges is essential to minimize false-negative results.
- “Nonsecretory” tumors may still be functional. Cluster 2 adrenergic tumors often exhibit minimal catecholamine secretion but contain dense intratumoral stores. Despite normal plasma catecholamine levels, elevated metanephrines provide a positive biochemical signal, indicating that these tumors are functional.
- Truly nonfunctional PPGLs are rare and biologically distinct. Most nonfunctional tumors occur in the head and neck and lack tyrosine hydroxylase expression. Rare abdominal nonfunctional PPGLs are often associated with *SDHB* variants and carry a higher metastatic risk.
- Functional status can be determined preoperatively. A positive correlation between the sum of plasma free metanephrines and tumor size strongly supports functional PPGL, whereas a large tumor without proportional elevation of plasma metanephrines raises suspicion for a truly nonfunctional lesion (particularly relevant for distinguishing early biochemically negative tumors from genuinely nonfunctional PPGL).

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A Structured Diagnostic Approach to Patients With Hypotonic Polyuria

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Differentiate among the main causes of hypotonic polyuria—arginine vasopressin deficiency (AVP-D, formerly central diabetes insipidus), arginine vasopressin resistance (AVP-R, formerly nephrogenic diabetes insipidus), and primary polydipsia (PP)—and explain the updated pathophysiology and nomenclature framework proposed in recent consensus statements.
- Apply a structured, stepwise diagnostic algorithm that integrates basal laboratory parameters (plasma sodium, osmolality, and copeptin) with dynamic testing, as indicated, to efficiently and accurately classify patients with hypotonic polyuria.
- Incorporate and interpret the newly validated clinical diagnostic score that combines basal sodium, osmolality, copeptin, and clinical variables to correctly identify AVP-D or PP, thereby reducing the need for stimulation testing.

Significance of the Clinical Problem

Hypotonic polyuria is an underrecognized clinical presentation in endocrinology and internal medicine, reflecting dysregulation of water homeostasis due to AVP-D, AVP-R, or excessive water intake. Although robust epidemiologic data on hypotonic polyuria itself are lacking, its typical biochemical counterpart—hyponatremia—accounts for 1% to 3% of hospital admissions. In contrast, disorders at the opposite end of the spectrum are far more common: hyponatremia, most often related to the syndrome of inappropriate antidiuresis (SIAD), is reported in 15% to 30% of inpatients, depending on the cohort and definitions used.¹⁻³

Accurate differentiation among AVP-D, AVP-R, and PP is critical, as misdiagnosis can have catastrophic consequences. Desmopressin administration in patients with PP may cause life-threatening hyponatremia, whereas delayed recognition of AVP-D can result in severe dehydration, hypernatremia, and neurological injury.⁴ Traditionally, diagnosis has relied on indirect physiological testing, such as the water-deprivation test, which is time-consuming, uncomfortable, and carries the risk of osmotic complications. The advent of assays measuring

copeptin, a stable surrogate marker of AVP secretion, has transformed the diagnostic landscape. Both basal and stimulated (hypertonic saline or arginine) copeptin measurements now provide rapid, safe, and accurate differentiation between the various causes of hypotonic polyuria, with diagnostic accuracy exceeding 90%.^{5,6} More recently, a COPEPTIN-based clinical diagnostic score has been proposed to integrate baseline plasma sodium (PNa⁺), plasma osmolality (POsm), and copeptin levels, in addition to clinical parameters, allowing precise classification of hypotonic polyuria without the need for dynamic testing in most patients.⁷ This structured approach minimizes risk, optimizes diagnostic efficiency, and enhances patient safety.

Beyond its diagnostic implications, understanding and managing hypotonic polyuria is increasingly relevant in the postoperative care of patients with pituitary and hypothalamic lesions, in whom transient or permanent AVP-D represents the most common electrolyte complication and is a predictor of prolonged hospitalization and morbidity.^{8,9} Early recognition through structured algorithms and copeptin-based strategies not only improves outcomes, but also aligns with the ongoing international effort to standardize terminology and promote safer care for patients with AVP-related disorders.^{10,11}

Practice Gaps

- Although copeptin-based tests have reshaped the diagnostic evaluation of patients with PP, only 2 copeptin assays have appropriate analytical precision and clinical data to support routine clinical use.
- Even when copeptin stimulation tests are available, logistical constraints can limit their clinical utility.
- Clinical misclassification persists when relying on water-deprivation tests, particularly in partial AVP-D and longstanding PP, where chronic medullary washout and decreased aquaporin-2 water channel synthesis can

blunt urine-concentrating ability and produce intermediate osmolality results.

- The stepwise approach using the clinical diagnostic score based on basal laboratory and clinical parameters offers practicality and accuracy but requires further real-world validation.
- Educational and nomenclature transitions add another layer of complexity.

Discussion

Despite major advances in copeptin-based diagnostics, several practice gaps continue to hinder optimal clinical implementation.

First, copeptin assays with proven technical reliability are not yet widely available. Currently, only 2 copeptin assays have the analytical precision and clinical data to support routine clinical use: the original sandwich immunoluminometric assay and its automated immunofluorescent successor on the KRYPTOR platform.¹² These assays are available only at a few reference centers, and many hospitals still rely on indirect physiological testing because copeptin measurements are not yet routinely reimbursed or integrated into diagnostic workflows—a challenge that is particularly relevant in low- and middle-income countries. In these settings, the classic water-deprivation test remains in use despite its modest diagnostic accuracy (70%-77%) and risk of osmotic complications.¹¹

Second, even when copeptin testing is available, logistical constraints can limit its clinical utility. Stimulated protocols (hypertonic saline or arginine infusion) require close monitoring, laboratory coordination, and specialized staff. Hypertonic saline testing, although considered the gold standard, carries risks of nausea, headache, vertigo, malaise, and significant hemodynamic shifts, and it requires exclusion of patients with cardiovascular or neurologic instability.¹³ Arginine-based stimulation is simpler and better tolerated than the hypertonic saline-based test; however, a recent head-to-head trial comparing the 2 tests showed diagnostic accuracy

of approximately 75% with arginine (cutoff 3.8 pmol/L [15.2 pg/mL]) vs 95% with hypertonic saline.⁶ Furthermore, the secretagogue arginine is not commercially available in several parts of the world.

Third, clinical misclassification persists, particularly in partial AVP-D and longstanding PP, where chronic medullary washout and decreased aquaporin-2 water channel synthesis can blunt urine-concentrating ability and produce intermediate osmolality results. The recently validated diagnostic score addresses this gap by integrating baseline laboratory parameters (PNa⁺, osmolality, and copeptin) and clinical parameters to predict AVP-D vs PP without stimulation testing.⁷ Notably, the diagnostic score differentiates AVP-D from PP with high accuracy and performs well even without basal copeptin measurement, with an area under the curve of 90% or higher in both the development and validation cohorts. However, external validation across diverse clinical contexts, including postoperative neurosurgical patients and critically ill cohorts, is still needed before widespread adoption.

Finally, educational and nomenclature transitions add another layer of complexity. The shift from “central diabetes insipidus” to AVP-D improves clarity and patient safety, yet many electronic health systems and clinical protocols still use outdated terminology, which can lead to prescription or communication errors in acute care. Bridging these gaps through broader laboratory access, clinician training, and standardized diagnostic algorithms is crucial to translating recent scientific advances into everyday endocrinology practice.^{10,11}

Clinical Case Vignettes

Case 1

A 32-year-old woman presents with a 2-year history of progressive thirst and marked polyuria (8–10 L/24 h), associated with fatigue, insomnia, and diffuse myalgia. She reports waking 3 to 4 times nightly to urinate and/or drink water. There is no history of pregnancy, head trauma, cranial

surgery, or visual changes. She does not consume excessive caffeine or alcohol. Family history is positive for hypertension and dyslipidemia. Physical examination reveals a BMI of 24.8 kg/m², blood pressure of 120/80 mm Hg, and pulse rate of 76 beats/min. There are no signs of dehydration or orthostatic hypotension.

Initial paired measurements obtained in May 2021:

PNa⁺ = 145 mEq/L (135–145 mEq/L)
(SI: 145 mmol/L [135–145 mmol/L])
POsm = 298 mOsm/kg (275–295 mOsm/kg)
Urine osmolality (UOsm) = 48 mOsm/kg
(300–900 mOsm/kg)

These tests are repeated later under similar conditions, confirming the presence of hypotonic polyuria with impaired urinary concentrating ability.

Question 1: Which of the following best defines hypotonic polyuria?

- A. Urine output >3 L/day with UOsm >600 mOsm/kg
- B. Urine output <2 L/day with POsm >295 mOsm/kg
- C. Urine output >3 L/day with UOsm <300 mOsm/kg
- D. Urine output >3 L/day with UOsm >800 mOsm/kg

Answer: C) Urine output >3 L/day with UOsm <300 mOsm/kg

Case 1, Continued

MRI of the hypothalamic-pituitary region demonstrates loss of the normal posterior pituitary T1-weighted hyperintensity and thickening of the pituitary stalk (*Figure 1, following page*). No mass lesion, optic chiasm compression, or hypothalamic extension is evident. The anterior pituitary gland appears morphologically preserved, and anterior pituitary hormone levels are within normal limits. Results of a combined outpatient and inpatient overnight indirect water-deprivation test (WDT) are summarized in *Table 1 (following page)*.

Table 1. Case 1 Water-Deprivation Test Results

Clock time	Time from start of water deprivation	Weight, kg	PNa ⁺ , mmol/L	POsm, mOsm/kg	UOsm, mOsm/kg	Urine volume, mL
07:00 (day before)	Baseline	72.5	140	293	82	
03:00	0 h	...	...	...	...	...
07:00	4 h	70.5	150	309	114	625
08:00	5 h	69.9 (↓3.6%)	151	315	163	550
10:00	7 h (2 h after intravenous desmopressin 2 mcg)	...	...	...	512	80

Clock time refers to local time; "Time from start of water deprivation" is counted from 03:00. Weight change is expressed relative to baseline (07:00, day before). Symbol: ↓, percentage change from baseline.

The WDT is planned as an overnight, combined outpatient and inpatient procedure. For safety reasons, she is instructed to begin water restriction at home at 3:00 AM (time 0 h) and then come to the hospital in the morning to complete the test under medical supervision.

Her body weight is 72.5 kg, and her 24-hour urine volume is 9.5 L (9500 mL/24 h).

The proposed equation to estimate the duration of water restriction required to achieve approximately 3% loss of body weight:

$$\text{Hours of projected water restriction} = \frac{\text{Weight (kg)} \times 0.03 \times 1000}{\text{Measured urine volume per hour (mL/h)}}$$

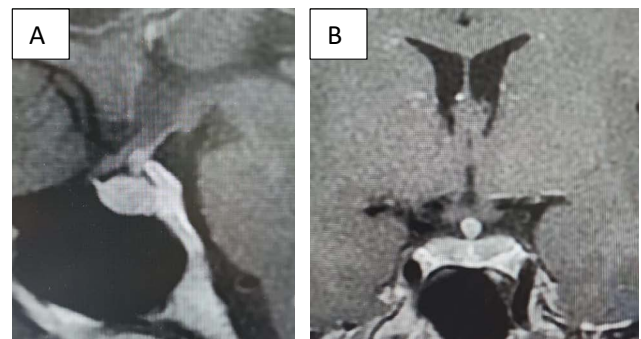
Question 2: According to this equation, what would be the approximate duration of water restriction expected for this patient?

- A. 1 hour
- B. 5.5 hours
- C. 8 hours
- D. 24 hours

Answer: B) 5.5 hours

Case 1, Continued

The indirect WDT was first described more than half a century ago¹⁴ and remained the diagnostic gold standard until recently.

Figure 1. Case 1 Sellar MRI

Panel A, Sagittal noncontrast T1-weighted image showing pituitary stalk thickening and absence of the normal posterior pituitary T1 hyperintensity ("bright spot"). Panel B, Coronal postcontrast T1-weighted image demonstrating focal sellar/suprasellar enhancement.

Question 3: All of the following statements are true concerning the interpretation of the indirect WDT, except:

- A. In patients with partial AVP-D and longstanding PP, urinary concentration after water deprivation is expected to increase to levels between 300 and 800 mOsm/kg
- B. An increase in urinary osmolality >9% upon desmopressin administration excludes the diagnosis of PP
- C. In patients in whom urinary osmolality remains <300 mOsm/kg during water deprivation but increases >50% following desmopressin administration, complete AVP-D can be diagnosed
- D. Copeptin measurement at the end of WDT has low diagnostic accuracy because most patients do not achieve hyperosmolality after fluid deprivation

Answer: B) An increase in urinary osmolality >9% upon desmopressin administration excludes the diagnosis of PP

Case 1, Continued

Question 4: According to the clinical probability score for AVP-D proposed by Atila et al,⁷ which combines basic laboratory parameters (PNa⁺, osmolality, and copeptin) with clinical variables (nocturia frequency, nighttime drinking, symptom onset, anterior pituitary dysfunction, and history of pituitary surgery), could the use of this score at presentation have obviated the need for a WDT in this patient?

- A. No—the patient's PNa⁺ and POsm were within the reference range, indicating low clinical probability and the need for dynamic testing
- B. No—stimulated copeptin testing is mandatory for all suspected AVP-related disorders, regardless of the clinical score
- C. Yes—the combination of high-normal PNa⁺ and POsm, marked nocturia (3 to 4 episodes nightly), and regular nighttime drinking places her in the high clinical probability category for AVP-D, even without a baseline copeptin measurement, making WDT unnecessary
- D. Uncertain—the clinical score is only validated in postoperative pituitary surgery cohorts and cannot be applied in this setting

Answer: C) Yes—the combination of high-normal PNa⁺ and POsm, marked nocturia (3 to 4 episodes nightly), and regular nighttime drinking places her in the high clinical probability category

for AVP-D, even without a baseline copeptin measurement, making WDT unnecessary

Case 1, Continued

The patient is subsequently enrolled in the CARGOx⁶ trial, a prospective multicenter study comparing osmotic and nonosmotic stimuli for copeptin release. Her basal, arginine- and hypertonic saline-stimulated copeptin levels are detailed in *Table 2*. Findings on further complementary image and laboratory workup are unremarkable, and a 6-month follow-up sellar MRI does not reveal progression of pituitary thickening, consistent with the diagnosis of infundibuloneurohypophysitis.

Question 5: In this patient, AVP-D has been confirmed by low basal and stimulated copeptin levels. According to current evidence, which of the following cutoff values best differentiates AVP-D from PP using hypertonic saline stimulation? And, in which scenario may arginine stimulation be considered as an alternative?

- A. Postsaline copeptin <4.9 pmol/L (<19.7 pg/mL) confirms AVP-D; arginine stimulation may be used when hypertonic testing is contraindicated or unavailable, in which case a copeptin value <3.8 pmol/L (<15.3 pg/mL) is suggestive of AVP-D
- B. Basal copeptin <6.5 pmol/L (<26.1 pg/mL) and postsaline <10 pmol/L (<40 pg/mL) confirm AVP-D; arginine should always replace hypertonic saline to reduce risk

Table 2. Baseline (After 2 Hours Water Restriction), Arginine-Stimulated, and Hypertonic Saline-Stimulated Copeptin, PNa⁺, and POsm Concentrations

Parameter	Baseline (2 h water restriction)	Arginine-stimulation test	Saline-stimulation test
Copeptin	1.8 pmol/L (7.23 pg/mL)	1.2 pmol/L (4.8 pg/mL)	0.8 pmol/L (3.2 pg/mL)
Na ⁺	144 mEq/L (144 mmol/L)	145 mEq/L (145 mmol/L)	150 mEq/L (150 mmol/L)
POsm	295 mOsm/kg	298 mOsm/kg	310 mOsm/kg

- C. Basal copeptin <2.6 pmol/L (<10.4 pg/mL) and postsaline >6.5 pmol/L (>26.1 pg/mL) confirms partial AVP-D; arginine is the gold standard for all cases
- D. Postsaline copeptin <21.4 pmol/L (<85.9 pg/mL) confirms AVP deficiency; arginine is contraindicated in postoperative patients

Answer: A) Postsaline copeptin <4.9 pmol/L (<19.7 pg/mL) confirms AVP-D; arginine stimulation may be used when hypertonic testing is contraindicated or unavailable, in which case a copeptin value <3.8 pmol/L (<15.3 pg/mL) is suggestive of AVP-D

Case 2

A 34-year-old woman is referred for evaluation of suspected AVP-D. Her medical history is notable for a diagnosis of Sheehan syndrome 6 months after a cesarean delivery. Combined pituitary hormone deficiency was confirmed, and treatment with levothyroxine, prednisone, and a combined oral contraceptive was initiated with subsequent clinical improvement.

The patient describes the onset of polyuria and polydipsia as insidious, beginning sometime after Sheehan syndrome was diagnosed. She reports nocturia (~2 episodes nightly) and polydipsia (~5 L of fluids/24 h) associated with drinking at night (<1 L per night). She has insomnia and

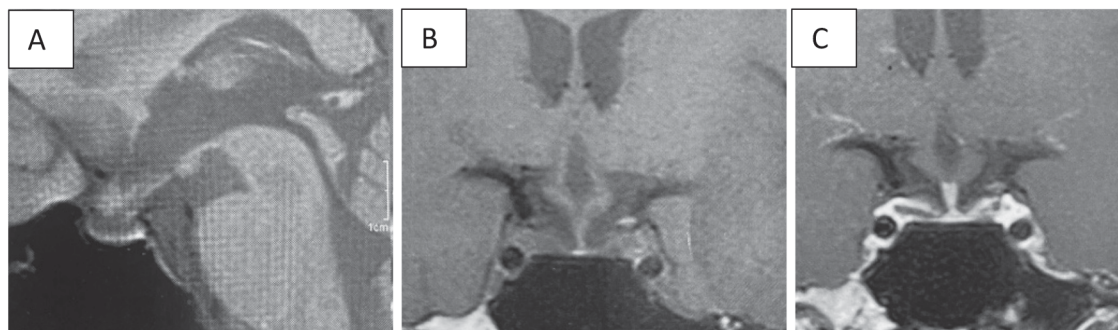
states that the frequency of nocturia and nighttime fluid intake fluctuates with her anxiety/insomnia status, with a few nights each week when she does not wake up at all. On physical examination, she appears well hydrated, with a normal heart rate and blood pressure and no postural hypotension. Her height is 61.8 in (157 cm), and weight is 134.7 lb (61.1 kg) (BMI = 24.8 kg/m²).

Baseline biochemical and hormonal results:

PNa⁺ = 141 mEq/L (135-145 mEq/L)
(SI: 141 mmol/L [135-145 mmol/L])
Plasma K⁺ = 3.7 mEq/L (3.5-5.1 mEq/L)
(SI: 3.7 mmol/L [3.5-5.1 mmol/L])
Glucose = 73 mg/dL (70-100 mg/dL) (SI: 4.1 mmol/L [3-9-5.6 mmol/L])
Creatinine = 1.02 mg/dL (0.6-1.2 mg/dL)
(SI: 90 μ mol/L [53-106.1 μ mol/L])
Total corrected calcium = 8.8 mg/dL (8.5-10.2 mg/dL) (SI: 2.2 mmol/L [2.1-2.55 mmol/L])
Cortisol = 0.7 μ g/dL (5-20 μ g/dL) (SI: 19.3 nmol/L [138-552 nmol/L])
ACTH = 5 pg/mL (3-45 pg/mL) (SI: 1.1 pmol/L [0.7-9.9 pmol/L])
Free T₄ = 1.07 ng/dL (1.05-1.56 ng/dL)
(SI: 13.8 pmol/L [13.5-20.1 pmol/L])
Prolactin = 4.8 ng/mL (2.8-18 ng/mL)
(SI: 0.2 nmol/L [0.12-0.78 nmol/L])
IGF-1 = 36 ng/mL (71-234 ng/mL) (SI: 4.7 nmol/L [9.3-30.6 nmol/L])
Urine volume = 370 mL/24 h (60.5 mL/kg per 24 h)
Urine creatinine = 1179 mg/24 h (19 mg/kg per 24 h)

Sellar MRI (Figure 2), performed in the early postpartum period, shows reduced pituitary

Figure 2. Sellar MRI in the Early Postpartum Period



Panel A, Sagittal T1-weighted image demonstrating reduced pituitary gland volume and a preserved posterior pituitary T1 hyperintensity ("bright spot"). Panel B, Coronal T1-weighted image. Panel C, Coronal postcontrast T1-weighted image showing homogeneous pituitary enhancement without a focal sellar lesion.

[Color—Print (Color Gallery page CG18) or web & ePub editions]

gland volume and a visible posterior pituitary bright spot.

Question 6: Based on the role of MRI in the diagnostic evaluation of patients with hypotonic polyuria, which of the following is correct?

- A. MRI of the sella is the gold-standard diagnostic tool in the evaluation of patients with hypotonic polyuria
- B. The addition of MRI data showed no major improvement in diagnostic accuracy of the novel diagnostic score for AVP-D recently proposed by Atila et al
- C. A preserved pituitary bright spot does not exclude AVP-D, as it may be seen in up to one-third of patients with AVP-D
- D. Pituitary stalk thickening is a more sensitive finding for AVP-D than the absence of the pituitary bright spot

Answer: C) A preserved pituitary bright spot does not exclude AVP-D, as it may be seen in up to one-third of patients with AVP-D

Although AVP-D is not a common manifestation of Sheehan syndrome, it has been described in a minority of affected patients and, when present, usually reflects a partial rather than complete defect in AVP secretion.^{15,16} In this patient, investigation for AVP-D was therefore pursued by measuring PNa⁺, POsm, and copeptin after 2 hours of water deprivation:

PNa⁺ = 137 mEq/L (SI: 137 mmol/L)
 POsm = 283 mOsm/kg
 Copeptin = 2.1 pmol/L (8.5 pg/mL)

To better integrate these data with the clinical picture, we applied the recently proposed clinical diagnostic score that combines biochemical (PNa⁺, POsm, and copeptin) and clinical variables (anterior pituitary deficiency, nocturia, nighttime drinking) to estimate the probability of AVP-D.⁷

In this patient, the equation yielded:

Score = (PNa⁺ × POsm / 100) + 0 (copeptin <4.9 pmol/L) + 50 (anterior pituitary deficiency) + 10 (nocturia twice/night)

Score = (137 × 283 / 100) + 50 + 10 = 387.7 + 60 = 447

This value lies at the proposed decision threshold (~447 points), suggesting that further diagnostic evaluation is required rather than relying solely on basal measurements.⁷

Case 2, Continued

Question 7: Considering this patient's clinical diagnostic score, which of the following is the best next diagnostic test to determine whether she has AVP-D?

- A. WDT followed by desmopressin administration
- B. Baseline copeptin measurement
- C. Copeptin measurement after hypertonic saline stimulation
- D. Copeptin measurement after arginine stimulation

Answer: C) Copeptin measurement after hypertonic saline stimulation

The patient underwent a hypertonic saline–stimulation test with copeptin measurement. Copeptin was measured by the immunofluorescent Kryptor assay when serum sodium reached 150 mEq/L (150 mmol/L), yielding a copeptin value of 5.5 pmol/L (22 pg/mL), consistent with PP. Behavioral therapy was recommended. At a follow-up visit 6 months later, the patient reported clinical improvement, with reduce water intake, particularly at night, and consequently, polyuria decreased.

Hypotonic polyuria is defined as urine output exceeding 40 to 50 mL/kg per day (~3 L/24 h in adults) with a UOsm less than 300 mOsm/kg. Accordingly, Answer C is the correct response to Question 1. This combination reflects the kidneys' impaired ability to concentrate urine in the setting of water imbalance. In both patients, UOsm was clearly below this threshold, confirming

true water diuresis rather than osmotic diuresis. Values between 300 and 600 mOsm/kg are indeterminate and may require dynamic testing. Conversely, a UOsm above 600 to 800 mOsm/kg indicates preserved urine-concentrating ability and generally argues against clinically significant AVP-D; if polyuria persists in this setting, osmotic diuresis or other secondary causes (eg, hyperglycemia, urea load, mannitol, sodium intake, hypercalcemia, hypokalemia, or chronic kidney disease) should be investigated.^{11,17}

Physiologically, polyuria may occur with either hypotonic plasma (as in PP) or hypertonic plasma (as in AVP-D or AVP-R). Nevertheless, most patients present with normal plasma tonicity because their compensatory thirst response is normal. Therefore, paired assessment of POsm and serum sodium is essential to define tonic status. A POsm greater than 300 mOsm/kg and/or PNa⁺ greater than 145 mEq/L (>145 mmol/L) indicates hypertonicity, strongly suggesting AVP-D or AVP-R in a patient with hypotonic polyuria. Values in the low-normal range are more compatible with PP.^{18,19} This simple step already narrows the differential diagnosis substantially, as illustrated by the high-normal POsm/Na⁺ profile in Case 1 and the low-normal values in Case 2.

Historically, the indirect WDT has been the cornerstone for distinguishing AVP-D, AVP-R, and PP.^{18,20} However, it is labor-intensive, uncomfortable, and potentially hazardous, particularly in patients with complete AVP-D, who may develop marked hyponatremia and dehydration.²⁰ The test requires close monitoring of body weight, serum sodium, and vital signs, and is often contraindicated in individuals with cardiovascular disease, seizure risk, or impaired thirst. Despite these drawbacks, in many centers—especially where copeptin assays or sophisticated stimulation tests are unavailable—the classic WDT remains the most accessible and practical tool for evaluating patients with polyuria-polydipsia syndrome.

In this context, adapting the WDT to a combined outpatient-inpatient protocol in adult patients offers practical advantages without compromising safety.²¹ By estimating the required

duration of water restriction individually based on body weight and 24-hour urine output, a substantial portion of the restriction can be performed at home, reducing hospital time and helping to overcome the difficulty of securing inpatient beds solely for functional testing. In Question 2, this corresponds to Answer B (~5.5 hours of projected water restriction). Nonetheless, overnight, unsupervised water deprivation should be used with caution, and hours of water deprivation should be individualized for every single patient, with special attention to those with severe polyuria and polydipsia or those with a history of psychiatric illness, who may demand closer supervision.

Case 1 demonstrates how this protocol can safely confirm complete AVP-D. During short-term water restriction, POsm and PNa⁺ rose into the hypertonic range (Na⁺ >145 mEq/L [>145 mmol/L]), with measurable weight loss. The test was stopped once predefined safety criteria were met. Desmopressin administration then produced a more than 2-fold increase in UOsm, from 163 to 512 mOsm/kg, accompanied by a marked reduction in urine volume. This robust concentrating response in a patient with hypotonic polyuria is characteristic of complete AVP-D.^{18,20} Requiring a caregiver, providing written instructions to stop the test in case of warning symptoms, and ensuring early return to the hospital for serial monitoring make the procedure less burdensome for the health system and more acceptable for adults with professional and family responsibilities, while preserving diagnostic accuracy.²¹

Nonetheless, the indirect WDT is frequently nondiagnostic in patients with PP or partial AVP-D, as these patients present with reduced urine-concentrating ability and produce intermediate osmolality results during dehydration. In a large, prospective, multicenter diagnostic study of 144 patients with hypotonic polyuria, the WDT correctly distinguished partial AVP-D from PP in only approximately 70% of patients.⁶ In this context, the incorrect (“except”) statement in Question 3 is Answer B, because a

modest rise in UOsm after desmopressin does not reliably exclude PP.

Beyond classic dehydration tests, the recent availability of copeptin assays has reshaped the diagnostic approach to polyuria-polydipsia syndrome. Copeptin, the C-terminal portion of pre-pro-AVP, is a stable surrogate marker of AVP secretion and can be reliably measured in peripheral blood.^{19,22} In the landmark study by Fenske et al, a baseline copeptin level less than 2.6 pmol/L (<10.4 pg/mL) after overnight water deprivation discriminated complete AVP-D from PP with high accuracy, whereas baseline values greater than 20 pmol/L (>80.3 pg/mL) identified AVP-R, reflecting preserved AVP release with renal resistance.²² A subsequent prospective study of 55 patients with PP showed that a single baseline copeptin level greater than 21.4 pmol/L (>85.9 pg/mL), without prior water deprivation, differentiated AVP-R from other etiologies with 100% sensitivity and specificity.²³ In a more recent cohort of 141 patients with hypotonic polyuria, the diagnostic accuracy of this prespecified morning (after overnight water deprivation) copeptin cutoff value of less than 2.6 pmol/L (<10.4 pg/mL) in identifying patients with complete AVP-D was approximately 80%.⁵ However, baseline copeptin levels alone are usually insufficient to distinguish PP from partial AVP-D, as there is substantial overlap in copeptin levels between the 2 groups. Nevertheless, very high basal values may still be diagnostically useful: in a recent pooled analysis of 2 international multicenter trials of patients with AVP-D and PP undergoing the hypertonic saline test, Atila et al showed that a baseline copeptin value greater than 5.6 pmol/L (>22.5 pg/mL) after 2 hours of water restriction identified PP with 100% specificity, providing a practical “rule-in” threshold for primary polydipsia.⁷

When stimulation testing is required, a hypertonic saline-stimulated copeptin value of 4.9 pmol/L or less (≤ 19.7 pg/mL) (prespecified cutoff) or less than 6.5 pmol/L (<26.1 pg/mL) (post hoc) confirms AVP-D with greater than 95% diagnostic accuracy. In the second patient, whose tonic status and clinical profile were equivocal,

hypertonic saline stimulation yielded a copeptin value of 5.5 pmol/L (22 pg/mL)—within the typical range of PP—thereby providing a definitive diagnosis without the need for prolonged dehydration.

For patients in whom hypertonic saline is contraindicated or poorly tolerated, such as those with uncontrolled hypertension, heart failure, or epilepsy, arginine stimulation (0.5 g/kg over 30 minutes) provides a safer, although slightly less accurate, alternative. Using the conventional diagnostic cutoff, a 60-minute post-arginine copeptin level below 3.8 pmol/L (<15.3 pg/mL) supports AVP-D, whereas values of 3.8 pmol/L or higher (≥ 15.3 pg/mL) are more consistent with PP.²⁴ In clinical practice, a 2-threshold approach may also be applied to increase diagnostic certainty: a post-arginine copeptin value of 3.0 pmol/L or less (≤ 12.1 pg/mL) can be used to “rule in” AVP-D with high specificity (~90%), while values of 5.2 pmol/L or greater (≥ 21 pg/mL) can “rule in” PP with similarly high specificity (>90%). Intermediate results should prompt confirmatory testing with hypertonic saline when feasible.²⁵ Notwithstanding, patients who develop severe nausea or vomiting during arginine stimulation may also be advised to undergo hypertonic saline stimulation for further evaluation.⁶ These stimulation-test thresholds correspond to Answer A in Question 5.

More recently, Atila et al proposed a practical diagnostic score that integrates clinical features, basal tonicity, and copeptin levels to differentiate AVP-related disorders early, thereby minimizing diagnostic delays and reducing the need for water-deprivation protocols.⁷ The score is calculated as the sum of: (a) basal PNa⁺ multiplied by POsm, divided by 100; (b) -50 points if plasma copeptin is greater than 4.9 pmol/L (>19.7 pg/mL); (c) +30 points for nocturia ≥ 3 times per night or +20 points for nocturia 2 times per night; (d) +20 points for sudden onset of polyuria or polydipsia; (e) +30 points for drinking more than 1 L during the night; (f) +50 points for anterior pituitary dysfunction; and (g) +50 points for a history of pituitary surgery. When applied to 2 independent

cohorts of patients with PP, a score above 441 points achieved an overall accuracy of 86% in diagnosing AVP-D. A high-specificity cutoff and a high-sensitivity cutoff were also identified: a score less than 415 points showed greater than 90% specificity for diagnosing PP, and a score greater than 461 points showed greater than 90% specificity for AVP-D. Interestingly, the accuracy of the diagnostic score without incorporating copeptin measurement was only slightly lower than the original score.⁷

Applying this tool to the patients in these vignettes highlights its strengths and limitations. In Case 1, the clinical score without copeptin already reached 465 points, placing her above both the overall best threshold (>441 points) and the high-specificity threshold (>461 points) for AVP-D. At this range, the score showed an ROC-AUC of 0.95, with specificity of 93% to 95% and sensitivity of 80% to 82% in the development and validation cohorts, indicating a high posttest probability of AVP-D even without dynamic testing. In practical terms, such a value would classify this patient as having a high clinical likelihood of AVP-D from the outset, and, according to the authors, could have obviated the need for a formal water-deprivation test in settings where the score has been implemented. Accordingly, this scenario corresponds to Answer C in Question 4. The case, therefore, illustrates how the combination of high-normal PNa⁺ and POsm and clinical parameters such as marked nocturia and nocturnal drinking yields a strongly positive clinical score that is concordant with the subsequent WDT and, more importantly, with the subsequent observed absence of copeptin response after arginine (1.2 pmol/L [4.8 pg/mL]) or hypertonic saline (0.8 pmol/L [3.2 pg/mL]) stimulation, reinforcing the validity of this tool as a front-line approach in centers where copeptin assays or standardized dynamic protocols are not readily available.

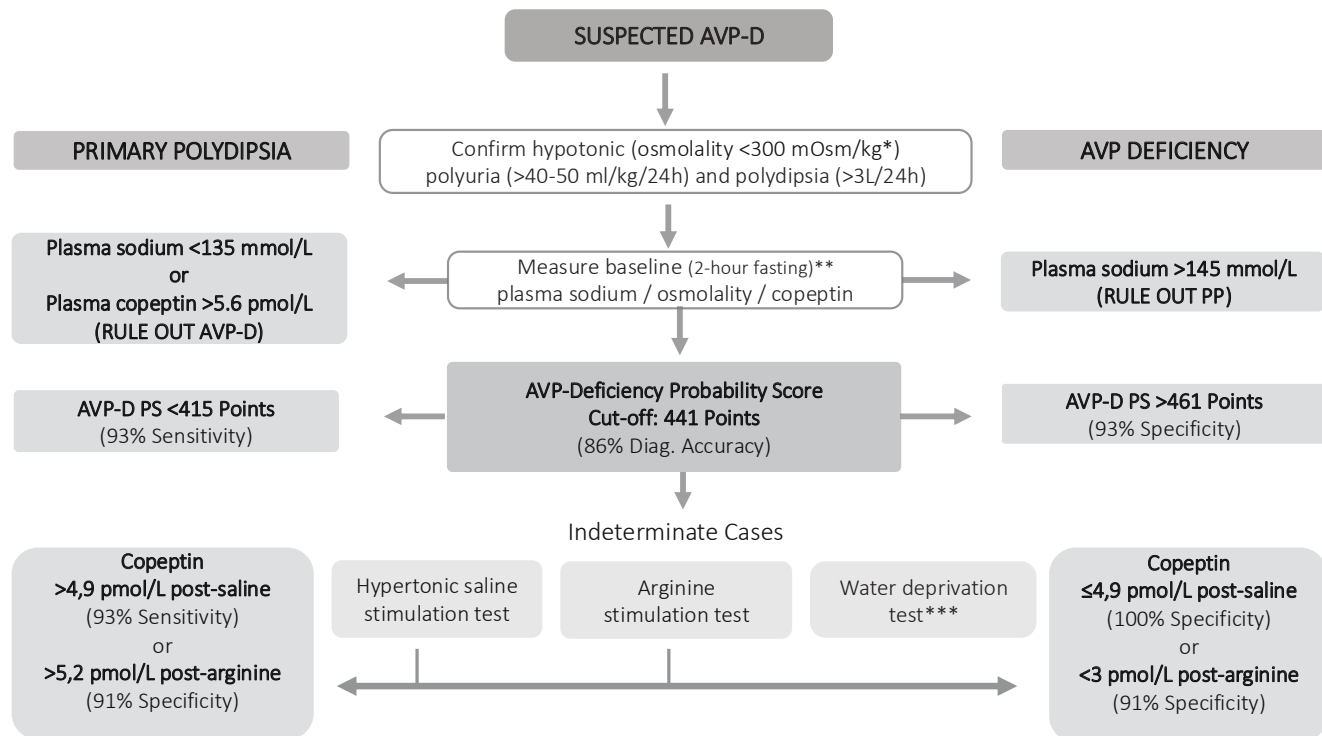
In Case 2, by contrast, the diagnostic score was borderline. The patient's total score was 447 points, just below the proposed overall best threshold for AVP-D (>447 points) and

between the high-sensitivity (≥415 points) and high-specificity (>461 points) cutoffs. As the authors suggest, patients with scores in this “gray zone” should undergo further evaluation with stimulation tests. Because the patient had no contraindications to undergoing hypertonic saline stimulation, the gold-standard test was performed, and the stimulated copeptin value of 5.5 pmol/L (22 pg/mL) confirmed PP. This corresponds to Answer C in Question 7.

MRI evaluation of the hypothalamic-pituitary region is an important diagnostic tool in the differential diagnosis of patients with hypotonic polyuria. Findings such as the absence of the posterior pituitary bright spot and/or a thickened pituitary stalk have previously been considered pathognomonic of AVP-D.¹³ Nevertheless, according to 2 recent multicenter international prospective diagnostic studies, the absence of the pituitary bright spot lacked both sensitivity and specificity for AVP-D, as it was visible in 30% to 33% of patients with AVP-D and absent in 14% to 39% of patients with PP. Accordingly, Answer C is the correct response to Question 6. Meanwhile, thickening of the pituitary stalk, when present, is a more specific finding, as it is observed in fewer than 5% of patients with PP.^{5,6} These findings highlight that MRI results must always be interpreted in the context of the clinical setting. Moreover, the addition of MRI data did not improve the accuracy of the novel diagnostic score proposed by Atila et al, which is notable given the high cost and limited availability of MRI.

Taken together, these illustrative cases highlight how modern diagnostic algorithms for polyuria-polydipsia syndrome integrate simple bedside information—24-hour urine output, paired POsm/Na⁺, and UOsm—with copeptin measurements, clinical scoring, and selected dynamic testing (*Figure 3, following page*).⁷ In resource-limited settings, a carefully supervised water-deprivation test remains an acceptable first-line tool, provided strict safety criteria and clear stop rules are followed. Where available, copeptin-guided diagnostic algorithms can replace traditional dehydration tests, improving accuracy,

Figure 3. Diagnostic Algorithm for Suspected AVP-D



reproducibility, and patient safety in modern endocrine practice.^{5-7,11}

Finally, these cases illustrate that no single test should be interpreted in isolation. Rather, the diagnosis of AVP-related disorders is based on the convergence of clinical features, tonic status, urinary concentrating capacity, copeptin responses, imaging findings, and, increasingly, validated diagnostic scores. This integrated strategy not only addresses the practical questions raised by each case but also provides a pragmatic framework for clinicians managing patients with hypotonic polyuria in everyday practice.

Key Learning Points

- Hypotonic polyuria requires early and precise etiologic classification. Differentiating AVP-D, AVP-R, and PP is critical, as misclassification can lead to severe complications, including life-threatening hyponatremia or hypernatremic dehydration.
- The classic water-deprivation test has important limitations. Although still useful in resource-limited settings, the indirect WDT is labor-intensive, uncomfortable, and often nondiagnostic—especially in partial AVP-D and longstanding PP—underscoring the need for safer, more accurate alternatives.
- Copeptin-based testing has transformed diagnostic accuracy. Basal and stimulated copeptin measurements, particularly after hypertonic saline stimulation, provide highly accurate differentiation among AVP-D, AVP-R, and PP, often eliminating the need for prolonged dehydration testing.
- Clinical diagnostic scores enable earlier, safer decision-making. Integrating simple biochemical parameters with key clinical features enables reliable patient stratification, often obviating dynamic testing and guiding the appropriate selection of stimulation protocols when needed.

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PEDIATRIC AND ADOLESCENT ENDOCRINOLOGY

Management of 46,XY Difference of Sex Development Across the Lifespan: A Multidisciplinary Team Perspective

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the biological basis of typical and atypical sexual development.
- Outline a systematic, empathetic approach to the prenatal diagnosis and neonatal assessment of a child with atypical genitalia.
- Describe the step-by-step diagnostic evaluation for a difference of sex development (DSD) based on karyotype.
- Discuss the complex, shared decision-making process for sex of rearing assignment within a multidisciplinary team.
- Formulate a management plan for the first years of life, including medical treatment, timing of surgery, and psychosocial support.
- Differentiate among common DSD etiologies (eg, congenital adrenal hyperplasia [CAH], complete androgen insensitivity syndrome [CAIS], 5 α -reductase deficiency, gonadal dysgenesis) using clinical cases spanning prenatal to adolescent presentations.
- Describe lifelong management of DSD, particularly 46,XY DSD, through a patient-centered journey.
- Establish precision diagnostics (using genetics, hormones, imaging).
- Engage in decision-making within a multidisciplinary team, guide timely and appropriate interventions, and offer unconditional psychosocial support to the patient and family.
- Help the individual live a full, dignified life with a solid identity, addressing more than just anatomical concerns.

Practice Gaps

- Lack of familiarity with the systematic diagnostic protocol for DSD and specific etiologies.
- Ineffective or harmful communication with families during the initial, critical moments of diagnosis and decision-making.
- Isolated decision-making by individual specialists instead of a coordinated,

multidisciplinary team approach that includes psychosocial support.

- Lack of a long-term perspective and failure to plan for pubertal development, transition to adult care, and the patient's future quality of life and gender identity.

Discussion

The birth of a child is a moment of great expectation for the family, and one of the first questions asked by parents and the health care team is, "Is it a boy or a girl?"^{1,2} The answer, based on observation of the external genitalia, immediately defines a series of social, cultural, and emotional expectations. When a newborn presents with genitalia that is not typically male or female, characterized as atypical genitalia or a DSD, this moment transforms into a medical and psychosocial emergency. This condition, previously referred to in pejorative or imprecise terms (intersex, pseudohermaphroditism), is now understood as a spectrum of conditions where chromosomal, gonadal, or anatomical development does not follow typical patterns. The approach to these children, especially during the critical period from prenatal suspicion to the first 2 years of life, requires multidisciplinary knowledge, extreme sensitivity, and a structured protocol that prioritizes the child's overall well-being and family support.

The objective of this chapter is to provide a practical, evidence-based guide to diagnostic, therapeutic, and psychosocial approaches for newborns and infants with atypical genitalia, informed by the latest evidence and international expert consensus. We will cover everything from the biological foundations of normal sexual development to the complex processes of shared decision-making, treatment, and initial follow-up, always emphasizing respect for diversity, the rights of the child, and the centrality of the family in care.

Fundamentals of Normal Sexual Development

To understand DSDs, it is essential to review the mechanisms underlying the formation of a typical sexual phenotype. This sequential and orchestrated process is divided into the following main stages: determination of chromosomal, gonadal, and phenotypic sex.

Determination of Chromosomal and Gonadal Sex

At the moment of fertilization, the combination of sex chromosomes (XX or XY) establishes the chromosomal sex. In humans, the presence of the *SRY* gene (sex determining region Y) on the Y chromosome is the main inducer of testicular differentiation from the bipotential gonad, around the 6th week of embryonic life. In the absence of *SRY*, the gonad differentiates into an ovary. This is the first major milestone: the formation of a testis or an ovary defines the gonadal sex.²

Phenotypic Differentiation: The Jost Model

Internal and external genitalia develop from embryonic structures common to both sexes: the wolffian ducts (male precursors) and müllerian ducts (female precursors), in addition to the genital tubercle, urogenital folds, and labioscrotal swellings. Phenotypic differentiation is hormonally directed, following the model described by Jost et al.³

Male development is an active process, dependent on hormones secreted by the fetal testis:

- *Antimüllerian hormone (AMH)*: Secreted by Sertoli cells, AMH promotes the regression of the müllerian ducts, preventing the formation of the uterus, fallopian tubes, and upper portion of the vagina.
- *Testosterone*: Produced by Leydig cells, testosterone promotes the stabilization and differentiation of the wolffian ducts into the epididymis, vas deferens, and seminal vesicles.
- *Dihydrotestosterone (DHT)*: DHT is a product of testosterone metabolism by the enzyme.

- *5 α -Reductase 2*: 5 α -Reductase 2 is responsible for the masculinization of external genitalia: growth of the phallus, fusion of the labioscrotal folds to form the scrotum, and formation of the penile urethra.

Female development mainly occurs without testicular influence. In the absence of AMH, the müllerian ducts persist and develop into the female internal structures (uterus, fallopian tubes, and upper vagina). Without androgen action, the genital tubercle develops into the clitoris, the urogenital folds form the labia minora, and the labioscrotal swellings give rise to the labia majora.

Although traditionally described as the “basic pattern” or default of human sexual development, the female phenotype results from an active network of molecular and genetic signals that promote the formation and maintenance of the ovary and female reproductive tract.^{4,5}

Hormonal Action and Pubertal Development

Androgens (testosterone and DHT) act by binding to a specific intracellular receptor called the androgen receptor (AR). This hormone-receptor complex then acts in the cell nucleus, regulating the expression of genes that lead to virilization. In addition to fetal differentiation, androgens are essential for sexual maturation during puberty, including the development of secondary sexual characteristics, growth of the penis and scrotum, increased muscle mass, deepening of the voice, and maintenance of sexual and metabolic function in adult life.

Female sex hormones, mainly estrogens and progesterone, exert their effects by binding to specific nuclear receptors, regulating gene transcription that coordinates female sexual development and maturation. The progressive increase in estradiol levels causes the development of secondary sexual characteristics, such as breast growth, redistribution of adipose tissue in a female pattern, and accelerated bone maturation. Additionally, estrogens support the maturation of the internal genitalia, vascularization, and the

vaginal epithelium, while progesterone, after ovulation begins, regulates the menstrual cycle and prepares the endometrium for pregnancy. Through the action of gonadotropins, FSH promotes the growth and maturation of ovarian follicles, while LH stimulates sex steroid production and, subsequently, ovulation.^{4,5}

Differences of Sex Development

During fetal development, sexual differentiation results from the precise interaction of chromosomal, gonadal, and hormonal factors, leading to the formation of internal and external genitalia. Alterations in any of these stages can cause variations in sex development, manifested as atypical genitalia. These changes can be detected prenatally through imaging or genetic testing or recognized at birth in the delivery room when the immediate determination of sex is called into question. Furthermore, other manifestations can appear later, such as during puberty, due to the absence or delay of secondary sexual characteristics, or even due to atypical pubertal signs. Infertility and symptoms of gonadal insufficiency also fall within this broad clinical spectrum. Given this scenario, it is essential to consider the diagnosis of DSD early, so the family can receive appropriate support even before birth, and the patient can access the best therapeutic and psychological management based on comprehensive care.

Prenatal Diagnosis (Box 1)

Advances in imaging and genetic techniques have enabled many DSDs to be diagnosed during intrauterine life. This early detection introduces a new scenario for the family, who must manage complex information even before birth. Anticipating the diagnosis allows for planning medical care and requires a support network to help family members understand the condition as they face feelings of uncertainty and anxiety.^{2,4,5}

Box 1. Approach in the Prenatal Period**Signs of DSDs in the Prenatal Period**

- Discordance between genital appearance on ultrasonography and fetal sexing (cell-free DNA)
- Atypical genitalia on ultrasonography

Acceptance and Clarification

- Avoid unnecessary invasive procedures
- Clarify and reassure the family
- Refer to a reference center
- Plan for presence of the team at delivery

At the Birth of the Baby

- Multidisciplinary team should be present
- Assessment of external genitalia at birth; guidance for parents regarding diagnostic possibilities and how to communicate with the family about the birth of a child with a DSD

Prenatal Suspicion Scenarios

Prenatal suspicion typically arises from 1 of 3 situations:

- **Discordance between fetal sexing and ultrasonography findings:** Determination of fetal sex by analysis of cell-free DNA in maternal blood (which identifies Y-chromosome sequences) may not correspond to the appearance of external genitalia visualized on second-trimester morphology ultrasonography.
- **Identification of atypical genitalia on ultrasonography:** An experienced ultrasonographer can identify atypical morphology of the external genitalia, such as a phallus with a labioscrotal cleft or clitoromegaly.
- **Family history of DSD.**

Conduct and Counseling in the Prenatal Period

The discovery of a possible DSD during pregnancy is a delicate moment that requires ethical and empathetic conduct.^{4,5}

- **Avoid unnecessary invasive procedures:** Amniocentesis or chorionic villus sampling should not be conducted solely to define the etiology of the DSD. The inherent risk of these procedures is not justified, as the initial

management in the neonatal period (especially screening for CAH) is the same, regardless of the prenatal molecular diagnosis.

- **Clarify and welcome the family:** The doctor should clearly and calmly inform the parents of the diagnostic suspicion, explaining that there is a variation in the baby's genital development that will be further investigated after birth. It is crucial to convey, whenever applicable, that the fetus's overall health is preserved. Additionally, it should be emphasized that a multidisciplinary team will be available to accompany the baby from the beginning, ensuring adequate assessment and specialized support for the family.
- **Referral and planning:** If the doctor is not experienced in managing DSDs, it is essential to refer the parents to a specialist (pediatric endocrinologist or geneticist) at a reference center for consultation. Birth planning should include the presence or immediate availability of a trained, multidisciplinary team to ensure adequate support for the newborn and comprehensive guidance for the family from the first moments.
- **Communication:** It is recommended to use expressions such as "difference or variation in genital development that we will need to assess after birth" instead of alarming, stigmatizing, or inaccurate terms like "anomaly" or "hermaphroditism." Communication should prioritize welcoming the family and planning care for the newborn, avoiding premature diagnostic speculations that may generate anxiety or misinterpretations.

Approach in the Delivery Room and Neonatal Assessment (Box 2)

Birth is the moment of greatest emotional impact. The first assessment and the first words said to the family are unforgettable and set the tone for the entire future relationship with the health care team.⁴

Box 2. Neonatal Evaluation (0-30 Days) and Minipuberty (1-6 Months)**Newborn With Atypical Genitalia or Male Genitalia and Bilateral Cryptorchidism****Emergent Screening for CAH (21-Hydroxylase Deficiency)**

- Measurement of 17-OHP, sodium, potassium, glucose
- Assess risk of adrenal crisis
- Research proteinuria through reagent strips for urine analysis (rule out Smith-Lemli-Opitz syndrome)

Initial Diagnostic Investigation

- Karyotype/array (or FISH/PCR for SRY or other Y-chromosome genes)
- Pelvic ultrasonography (assess presence of uterus, gonads)
- Baseline hormonal measurements
- AMH, testosterone, DHT
- LH, FSH, 17-hydroxypregnenolone, 17-OHP, progesterone, 11-deoxycortisol, androstenedione, cortisol

Abbreviations: FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction; 17-OHP, 17-hydroxyprogesterone.

Initial Physical Examination

When called to assess a newborn with atypical genitalia, the professional should perform a thorough physical examination and record findings in the chart.

- *Phallus measurement:* Measure the penile length with the penis stretched and its diameter. In full-term newborns, micropenis is defined as a stretched length of less than 2.5 cm. Classify the degree of virilization (Sinnecker classification).
- *Urethral assessment:* Identify the location of the urethral meatus. Proximal or penoscrotal hypospadias are common signs of genital hypovirilization.
- *Identification of perineal orifices:* Check for a single urogenital opening (urogenital sinus) or separate orifices (vaginal and urethral). It is emphasized that, in many cases, differentiation between the 2 orifices cannot be made by visual inspection alone. In these situations, it is necessary to await the surgical procedure, during which urethral probing will enable anatomical confirmation.

- *Palpation of gonads:* Evaluate the presence, size, and consistency of gonads in the inguinal canals or in the scrotal/labial bag. Palpable gonads strongly suggest the presence of testicular tissue.
- *Assessment of fusion of labioscrotal folds:* Observe the degree of fusion of the folds.
- *Assessment of associated dysmorphisms:* Evaluate characteristics suggestive of genetic syndromes (eg, webbed neck, edema of hands and feet, and low hairline [often related to Turner syndrome]).
- *Signs of CAH:* Assess for skin hyperpigmentation (especially genitals and nipples), recurrent vomiting, lethargy, difficulty sucking, weight loss, complete virilization (Prader V) without palpable gonads.⁶
- *Presence of inguinal hernia:* Assess for inguinal hernias in patients with female external genitalia (suspicion of CAIS).

Directed Family History

A directed family history should be taken to evaluate for consanguinity, history of unexplained neonatal deaths, infertility, atypical genitalia, or hirsutism in the family. Family history is fundamental to identifying patterns of genetic inheritance (eg, autosomal recessive, X-linked).

Initial Communication With Parents

Choosing the first words is a critical skill. The approach should be calm, empathetic, and confident.

- *Recommended guiding phrase:* “Congratulations on the birth of your baby! During the exam, I noticed that the formation of your baby’s genitals is not completely typical. This means we will need to do some specific tests in the next hours and days to better understand how it developed. It is important to know that this is not an emergency nor something that puts the baby’s life at risk at this moment. We are

here to investigate together calmly and clarify all your doubts.”⁷

- *What to avoid:* Do not assign a sex (“your son,” “your daughter”). Do not use terms such as “abnormal,” “defect,” or “hermaphrodite.” Do not make assumptions or give false guarantees about the future.
- *Guide the team:* It is the duty of the lead physician to ensure the entire team (nursing staff, residents) uses the same neutral, welcoming language and refers to the baby by name (if already given) or simply as “the baby.”

Emergent Laboratory Screening

In newborns with atypical genitalia and bilateral cryptorchidism, the immediate priority is to rule out salt-wasting CAH due to 21-hydroxylase deficiency. This condition represents the most frequent cause of virilization in 46,XX individuals and can rapidly progress to a potentially fatal adrenal crisis in the first weeks of life. Initial laboratory tests include measuring 17-hydroxyprogesterone (17-OHP), serum sodium, serum potassium, plasma glucose, and arterial or venous blood gas (if there are signs of shock).

If there is clinical or laboratory suspicion of salt-wasting CAH (very high 17-OHP, low sodium, and high potassium), immediate treatment should be initiated with intravenous hydrocortisone and volume replacement with 0.9% saline, without waiting for complete diagnostic confirmation.

Systematic Diagnostic Evaluation (Box 3)

After initial stabilization, a protocolized evaluation should begin to establish an etiological diagnosis, which will serve as the basis for all future decisions.

Mandatory Initial Exams

- *Cytogenetic study; karyotype/array or polymerase chain reaction amplification of the SRY gene/other Y-chromosome genes:* Cytogenetic analysis is the cornerstone and defines whether the pattern is 46,XX, 46,XY, or mosaic (eg, 45,X/46,XY). Amplification of the SRY gene and/or other

Box 3. Who Should Be Evaluated for DSDs and How to Evaluate in Childhood/Prepuberty

Children with atypical genitalia or with male genitalia and bilateral cryptorchidism or with female genitalia and uni or inguinal hernia and/or palpable gonad

Diagnostic Evaluation

Karyotype/Array (or FISH/PCR for SRY and Other Y-Chromosome Genes)

Ultrasonography

- Pelvic (uterus, gonads)
- Inguinal and scrotal/labia majora—identify gonads
- In case of doubt, request pelvic MRI (location and morphology of gonads)

Hormonal Measurements

- Sodium, potassium, AMH
- Assessment of adrenal steroids—17-hydroxypregnenolone, progesterone, 17-OHP, androstenedione, testosterone, aldosterone, renin, 11-deoxycortisol, cortisol (ACTH)
- Assessment of gonadal steroids—prolonged stimulation test with hCG, or recombinant LH—testosterone, DHT (testosterone-to-DHT ratio), 17-hydroxypregnenolone, 17-OHP, progesterone, androstenedione (androstenedione-to-testosterone ratio)

Y-chromosome genes is faster (results within hours) and can provide an initial indication of the presence of Y-chromosome material. It can be done on cells from an oral mucosal swab or blood.

- *Pelvic and kidney ultrasonography:* Evaluates the presence and morphology of the uterus. The presence of a uterus practically rules out diagnoses such as CAIS, the most common cause of 46,XY DSD. Ultrasonography also assesses the kidneys (associated anomalies are common in some syndromes) and can locate gonads.
- *Hormonal measurements:*
 - LH, FSH, and gonadal hormones: Baseline measurements are done during the mini-puberty period (2nd–6th month of life).^{2,4,5} In childhood, measurements are done after stimulatory testing of Leydig cells with hCG/recombinant LH.
 - AMH: AMH is an excellent marker of the presence and function of testicular tissue.

High levels indicate the presence of testes; undetectable levels suggest anorchia or gonadal dysgenesis.^{4,5}

- Testosterone and DHT: A high testosterone-to-DHT ratio (>26) suggests 5 α -reductase type 2 deficiency, although a normal ratio does not rule out this diagnosis.
- 17-Hydroxypregnenolone, progesterone, 17-OHP, androstenedione, cortisol, ACTH: These hormones should be measured to evaluate for CAH and other steroidogenesis defects.
- Urinary and serum steroid profile (by mass spectrometry): High-throughput mass spectrometry can identify profiles suggestive of inborn errors of steroidogenesis.

Diagnostic Flow Based on Karyotype

The investigation follows different paths depending on the karyotype result.

Karyotype 46,XX (Virilization of a Female Fetus)

The focus is to identify the source of androgens.

- First hypothesis = CAH: 21-Hydroxylase deficiency is the most frequent cause of CAH (90%-95% of cases). Evaluation should also be done to detect rarer forms of CAH (11 β -hydroxylase deficiency, 3 β -hydroxysteroid dehydrogenase deficiency type II, cytochrome P450 oxidoreductase [POR] deficiency).
- Second hypothesis = Androgens of maternal origin: Investigate the history of androgen use during pregnancy and the possibility of virilizing maternal tumors (eg, luteoma).
- Third hypothesis = 46,XX ovotesticular DSD and placental aromatase deficiency: These are rare diagnoses but need to be ruled out. An important difference between these conditions and CAH in prepubertal girls is the absence of virilization signs or androgen effects before puberty.

Karyotype 46,XY (Incomplete Masculinization of a Male Fetus)

The challenge is greater in this scenario, as the etiologies are more diverse. The evaluation seeks to differentiate defects in testosterone production, in its metabolization into DHT, or in their action (androgen receptor defects).

- Low AMH, high LH and FSH: Suggests gonadal dysgenesis (inadequate testicular development).
- Low testosterone, poor response to hCG stimulation: Suggests defect in testosterone synthesis (eg, 17-hydroxylase deficiency, 17,20-desmolase defect, 17 β -hydroxysteroid dehydrogenase type 3 defect).
- Normal or high testosterone, female or atypical genitalia: If the testosterone-to-DHT ratio is high, consider 5 α -reductase type 2 deficiency. It is important to remember that about 20% of individuals with pathogenic variants in the 5 α -reductase type 2 gene have a normal testosterone-to-DHT ratio.^{4,5}
- Normal or low AMH, uterus present: Suggests a defect in AMH production or action (persistent müllerian duct syndrome).

Karyotype With Mosaicism or Aneuploidy (eg, 45,X/46,XY)

Karyotypes with mosaicism or aneuploidy indicate chromosomal DSD (complete gonadal dysgenesis [resulting in female genitalia] or partial [causing atypical genitalia]). The phenotypic presentation is extremely variable, ranging from a female phenotype to an atypical male phenotype. The risk of gonadal tumor (gonadoblastoma) is increased, influencing management.^{4,5}

Molecular Genetic Studies

Next-generation sequencing (gene panels or exome) has revolutionized the diagnosis of DSDs, especially 46,XY DSDs.⁴⁻¹⁴ It enables detection of pathogenic variants in genes involved in gonadal determination, steroidogenesis, and hormonal action. A precise genetic diagnosis:

- Confirms the etiology.⁴⁻¹⁴
- Is fundamental for making an informed decision regarding sex assignment.
- Can inform about fertility prognosis and tumor risk.
- Allows family genetic counseling and evaluation of asymptomatic carriers.

Sex of Rearing Assignment: Multidisciplinary and Shared Decision-Making

This is the most complex and important decision in initial management. It should not be made by a single professional or under unnecessary time pressure. The goal is to assign a sex that maximizes the likelihood of a stable gender identity, satisfactory sexual function, and psychosocial well-being throughout life.^{4,5,15}

The Multidisciplinary Team

The decision should be made after discussion by a team that includes, at a minimum:

- Pediatric endocrinologist (often the process coordinator)
- Pediatric surgeon/pediatric urologist with experience in genitoplasty
- Psychologist/psychiatrist with knowledge of DSDs and gender development
- Clinical geneticist
- Social worker
- Specialized nurse

Criteria for the Decision

The team considers a set of factors, weighing them for each individual case:

- *Etiological and molecular diagnosis:* This is the most important factor. Understanding the specific clinical condition enables decisions to be based on published data on individuals' evolution into adulthood.⁴⁻¹⁴
- *Genital anatomy and surgical potential:* Assess whether the genitalia can be reconstructed to function properly and with good sensitivity for one sex or the other. Phallus size, long overvalued, should not be the sole determining factor.⁶
- *Fertility potential:* Whenever possible, the assignment that preserves the potential to have biological children should be prioritized. Advances in assisted reproductive techniques (such as intracytoplasmic sperm injection) have expanded possibilities.
- *Need for lifelong hormone therapy:* Assess the ease and adequacy of the hormonal replacement necessary to induce and maintain puberty according to the assigned sex.^{4,5,15-17}
- *Family opinion and context:* The final decision belongs to the parents. The team recommends, explains, and clarifies but does not impose. It is crucial to understand the family's cultural and religious context and expectations.

Process of Communication and Informed Consent

The discussion with parents should be held in one or more formal meetings, with time and privacy.

- *Explain the diagnosis:* Use accessible language, drawings, and models. Explain "how it happened."
- *Present the options:* Explain the pros and cons of each path (male or female) for that specific case, based on the above criteria.
- *Reveal uncertainties:* Be honest about what cannot be predicted with 100% certainty, such as future gender identity.
- *Listen actively:* Allow parents to express their fears, desires, and doubts.¹⁵
- *Reach a consensus:* The decision should be recorded as a shared informed consent.

Conduct in the First Years of Life

Once the sex of rearing is assigned, an integrated care plan begins that includes clinical treatment, surgery (when indicated), and intensive support.

Clinical Treatment

- *CAH:* Treatment is lifelong to prevent crises, avoiding hypocortisolism with adequate control of hyperandrogenism.¹⁵⁻¹⁹
- *Hydrocortisone:* Dosage of 10-15 mg/m² per day, divided into 3 doses.
- *Fludrocortisone:* 100-300 mcg daily for newborns, with progressive adjustment based on blood pressure and levels of renin, sodium, and potassium.
- *Sodium chloride:* 1-3 g daily supplement in the first year between feedings; breast milk has little sodium.
- *Family education:* It is essential to teach parents to administer medication, recognize signs of crisis (eg, vomiting, dehydration), and to double/triple the hydrocortisone dose in stressful situations (eg, fever, trauma, surgery). Providing an emergency letter and an intramuscular hydrocortisone injection kit is mandatory.¹⁹
- *Androgen replacement in 46,XY:* In a newborn assigned male, 2 to 3 injections of testosterone or topical DHT gel can be used in the first years of life and during childhood to promote penile growth, facilitating future surgeries.

Surgical Intervention^{20,21}

Surgery is a sensitive topic. The current principle is to perform surgery at the most appropriate time, by the most experienced surgeon. The period between 6 and 24 months of age is considered by many to be the ideal window for necessary surgeries, as it precedes the formation of more defined body awareness and the fixation of gender identity.

Feminizing Surgery

- *Objective:* Create genitalia of typical female appearance, with preserved clitoral sensitivity and vaginal orifice separate from the urethra.^{6,20}
- *Technique:* Clitoroplasty preserving the ventral and dorsal neurovascular bundles is the gold standard. Mobilization of the urogenital sinus and vaginal reconstruction/introitooplasty.
- *Controversy:* There is a movement advocating for postponing all surgeries until individuals reach the age of consent. However, the current consensus position recognizes that early surgery, when well performed, can avoid significant psychosocial stigma, and most adult patients with CAH operated on late express their wish to have been operated on earlier.

Masculinizing Surgery

- *Objective:* Correct hypospadias, perform orchiopexy for cryptorchidism, and construct a neourethra.²¹
- *Indication:* Correction of severe hypospadias is generally recommended before school age to adapt the genitals for standing urination.
- *Gonadectomy:* Indicated when the gonads are dysgenetic (high tumor risk, such as gonadoblastoma) or are incongruent with the assigned sex (eg, testes in a child raised as a girl, except in CAIS, where orchiectomy can be postponed until after puberty, when, after clarification, the child and family choose this option).¹⁸⁻²⁰

Psychosocial Support and Family Education

This pillar is as important as medical and surgical treatment.^{2,23,24}

- *Continuous psychological support:* Parents need space to grieve the child they expected, deal with anxiety, and learn to love and accept their child as he/she is. Psychological follow-up should begin at diagnosis and extend for years.

- *Education about the condition:* Parents should become experts in their child's condition. The team should provide written information, guidance manuals, and reliable websites, and connect them to support groups when available.
- *Communication with the child and the world:* Parents should be guided to:
 - Avoid creating secrets. The child should grow up knowing about their condition in an age-appropriate manner.
 - Use positive language ("your body developed in a different way") and avoid terms such as "disease" or "defect."
 - Know how to answer questions from family and friends, protecting the child's privacy but without feeding taboos.
- *Normalization of life:* Encourage parents to treat the child like any other child: play, stimulate, send to school, without overprotecting.

Follow-up and Transition (Box 4)

Follow-up of the child with DSD is a long-term commitment.

- *Regular consultations:* In the first year, consultations are more frequent (weekly/monthly/quarterly), for medication adjustment (CAH), growth monitoring, and psychosocial assessment. Later, consultations become semi-annual/annual.
- *Monitoring of pubertal development:* In preadolescence, assessment for the onset of puberty begins. Hormone therapy for pubertal induction (estrogen or testosterone) is started at the appropriate time, simulating the normal timing of puberty.^{4,5}
- *Progressive disclosure to the child:* As the child grows, new information about his/her condition, fertility, and sexuality is shared in an age-appropriate manner, always with the psychologist's support.

Box 4. Who Should Be Evaluated for DSDs and How to Evaluate After Pubertal Age

- Absence of breast development
- Spontaneous breast development with absence of menarche
- Presence of atypical genitalia or female genitalia with or without signs of virilization

Diagnostic Evaluation

- Karyotype/array (or FISH/PCR for SRY and other Y-chromosome genes)
- Pelvic ultrasonography (assess for presence of uterus, gonads)
 - Pelvic MRI (location and morphology of gonads)
- Baseline hormonal measurements
 - Sodium and potassium (rule out hypokalemia associated with 17-hydroxylase deficiency), AMH
 - Assessments of adrenal steroids—17-hydroxypregnenolone, progesterone, 17-OHP, androstenedione, testosterone, aldosterone (renin), 11-deoxycortisol, cortisol, ACTH
 - Assessment of baseline gonadal steroids—testosterone DHT (testosterone-to-DHT ratio), 17-hydroxypregnenolone, 17-OHP, progesterone, androstenedione (testosterone-to-androstenedione-ratio)
- Molecular studies to confirm or define etiological diagnosis

- *Preparation for transition:* In late adolescence, a structured plan to transition from pediatric care to the adult team (endocrinologist, gynecologist, urologist) begins, empowering the young person to become the manager of their own health.

Conclusion

The approach to the newborn and child with atypical genitalia is one of the most complex and rewarding challenges in medicine. It requires perfect integration between cutting-edge science (molecular genetics, endocrinology), refined technique (reconstructive surgery), and profound humanism (psychology, communication, ethics).

There are no ready answers or rigid protocols that work for everyone. Each child is unique, each family has its values, and each diagnosis carries its own implications. The path outlined in this chapter—based on accurate diagnosis, shared

multidisciplinary decision-making, appropriate treatment at the right time, and unconditional psychosocial support—provides the structure for the child to develop not only with functional genitalia but, above all, with self-esteem, a solid identity, and the ability to have a full, happy, and dignified life.^{25,26}

The role of the doctor and the health care team is to serve as a guide, facilitator, and support system.¹⁸ With humility to recognize uncertainties, empathy to welcome anguish, and competence to offer the best possible care, we can transform an initial moment of crisis and doubt into a journey of acceptance, love, and discoveries for the child and their family.

Clinical Case Vignettes

Case 1

A healthy 32-year-old woman (G1, P0) undergoes routine prenatal cell-free DNA screening at 10 weeks' gestation, which indicates a high probability of a 46,XY karyotype. Subsequent morphology ultrasonography at 18 and 22 weeks' gestation shows normal male internal structures but reveals female-typical external genitalia. No uterus is visualized. The pregnancy is otherwise uncomplicated. At term, the newborn is healthy with completely female-typical external genitalia. No gonads are palpable. Postnatal karyotype confirms 46,XY. Hormonal assessment on days 2 to 3 shows elevated AMH and high-normal LH and testosterone levels. Pelvic ultrasonography confirms the absence of a uterus and identifies 2 small structures in the inguinal canals. Genetic testing reveals a hemizygous pathogenic variant in the *AR* (androgen receptor) gene.

Which of the following is the most appropriate next step in the immediate postnatal management of this newborn?

- A. Schedule immediate bilateral gonadectomy to prevent malignancy
- B. Reassure the family and discharge the infant with a plan for vaginal dilation therapy in adolescence

- C. Register the infant as female and provide multidisciplinary counseling regarding the diagnosis of CAIS
- D. Initiate a trial of topical testosterone to assess androgen responsiveness
- E. Perform pelvic MRI to better characterize the gonads before discussing the diagnosis with the family

Answer: C) Register the infant as female and provide multidisciplinary counseling regarding the diagnosis of CAIS

The clinical, hormonal, and genetic findings are diagnostic of CAIS. Infants with CAIS are typically raised as female, which aligns with the female-typical genitalia. Immediate, clear, and supportive communication by a multidisciplinary team is the basis of initial management. While gonadectomy is often discussed, it is not immediate. Current guidelines support delaying gonadectomy until after puberty to allow for spontaneous pubertal development and patient involvement in the decision.

Case 2

A 14-year-old individual, raised as a girl, is brought to the clinic by their parents, who are concerned about the patient's refusal to live as a girl and increasing social withdrawal. The patient was born in a rural area, had "slightly atypical" genitalia, and was assigned female without further evaluation. The patient states, "I have always felt like a boy." On physical examination, the patient has no breast development, a deepened voice, and a 5.5-cm phallus with a single urogenital sinus opening. Bilateral gonads are palpable in the labioscrotal folds. Pelvic ultrasonography shows no uterus. Karyotype is 46,XY. Baseline hormone levels reveal an adult male-range testosterone concentration (400 ng/dL [13.9 nmol/L]) and a low DHT concentration (5 ng/dL [0.17 nmol/L]), resulting in a testosterone-to-DHT ratio of 33. Genetic testing confirms biallelic pathogenic variants in the *SRD5A2* gene.

According to the current literature, what is the approximate frequency of a female-to-male gender identity change in individuals with 5 α -reductase type 2 deficiency?

- A. Less than 10%
- B. Around 25%
- C. Around 60%
- D. More than 90%
- E. The frequency is dependent on the degree of external genitalia virilization at birth

Answer: C) Around 60%

Studies on 5 α -reductase type 2 deficiency cohorts have consistently shown a high rate of gender role change from female to male, particularly around puberty, occurring in approximately 50% to 60% of individuals. While the degree of genital virilization at birth can vary, the high frequency of gender role change in this specific condition is often independent of the initial degree of masculinization. The diagnosis of 5 α -reductase type 2 deficiency is a strong predictor of male identity, and the assignment of male sex is the best proposal for an affected newborn.

Case 3

A 16-year-old individual, raised as a girl since birth, is referred to the adolescent DSD clinic due to a lifelong sense of being male, which has intensified with puberty. Birth history revealed “slightly atypical” genitalia, for which no evaluation was performed. On physical examination, the patient has breast development (Tanner stage 3), no menarche, mild clitoromegaly, and partial labial fusion. Psychological assessment confirms gender dysphoria. Karyotype is 46,XY. Hormonal profile shows low testosterone, low estradiol, and elevated LH and FSH levels. Pelvic ultrasonography reveals bilateral small gonads and a small infantile uterus. A multigene panel identifies a heterozygous pathogenic variant in the *NR5A1* gene. The patient undergoes a bilateral gonadectomy and hysterectomy, which confirms dysgenetic gonads

without evidence of malignancy. The patient has now changed his name and legal documents to male and is very happy.

Following gonadectomy and in the context of a confirmed male gender identity, what should be the initial step in this patient’s medical management?

- A. Schedule a multistage genitoplasty and testicular prosthesis placement
- B. Initiate testosterone replacement therapy in progressive doses, mimicking normal male puberty, to induce and maintain virilization
- C. Refer the patient for a consultation with a fertility specialist
- D. Discharge the patient from regular follow-up, as the gonads were removed
- E. Recommend a psychological evaluation to reassess the stability of his gender identity

Answer: B) Initiate testosterone replacement therapy in progressive doses, mimicking normal male puberty, to induce and maintain masculinization

The patient has had a gonadectomy and now has hypergonadotropic hypogonadism, meaning his body no longer produces sex hormones. The immediate medical need is to initiate hormone replacement therapy (testosterone) to induce and maintain male secondary sexual characteristics, support bone health, and improve overall well-being.

Key Learning Points

- The treatment of an individual with a DSD requires a multidisciplinary team.
- The initial information provided is very important and is remembered forever; use few and correct words and refer the family to a DSD specialist.
- Treat the individual with transparency and without secrets and advise the family to do the same.

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Management of Hyperphagia in Prader-Willi Syndrome and Other Monogenic Obesity Syndromes

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe recommended dietary interventions for obesity caused by Prader-Willi syndrome (PWS).
- Identify appropriate indications for the use of diazoxide choline continuous release (DCCR) therapy for hyperphagia caused by PWS.
- Determine when to consider the use of GLP-1 receptor agonists for monogenic obesity and when to use setmelanotide therapy.

Significance of the Clinical Problem

Genetic obesity syndromes are typically associated with a combination of low metabolic expenditure and hyperphagia (lack of satiety), which results in obesity-related comorbidities that are extremely difficult to manage effectively. Hyperphagia negatively affects the quality of life for these patients and their families.^{1,2} For individuals with cognitive delays and hyperphagia, families often need to implement environmental restrictions to limit access to food, such as physically blockading the kitchen or locking cabinets, refrigerators/freezers, and garbage. Many higher-functioning

individuals with hyperphagia create their own environmental restrictions to avoid severe overeating and worsening obesity. These strategies can include having someone shop for groceries daily so there is no excess or tempting food in the home; not having personal transportation so it is difficult to get to food; and even using service animals to prevent them from leaving the home to buy food.

Many short-term phase 2 medication trials to treat hyperphagia in these conditions have shown promising results, only to be followed by failures in larger, longer-term clinical trials. Thus far, only a few medication trials have succeeded in achieving long-term management of these complex genetic metabolic conditions. This chapter focuses on recommended dietary interventions and on 2 medications that have shown success in clinical trials: DCCR and setmelanotide. Additionally, the potential use of GLP-1 receptor agonists is discussed.

Practice Gaps

- Traditionally, calorie-restricted diets are recommended for patients with hyperphagia and hypothalamic obesity. These diets can worsen appetite by limiting calories in people who perceive they are starving because of their condition.

- With an FDA-approved medication now available to treat hyperphagia in PWS, physicians may be tempted to use it for the most severe cases of this syndrome. However, this can be unsafe given the medication's well-known adverse effect profile.
- GLP-1 receptor agonists are effective in reducing appetite and weight in patients with environmental obesity, and many physicians believe these medications should be equally effective for patients with hyperphagia due to hypothalamic dysfunction; however, this is often not the case.

Discussion

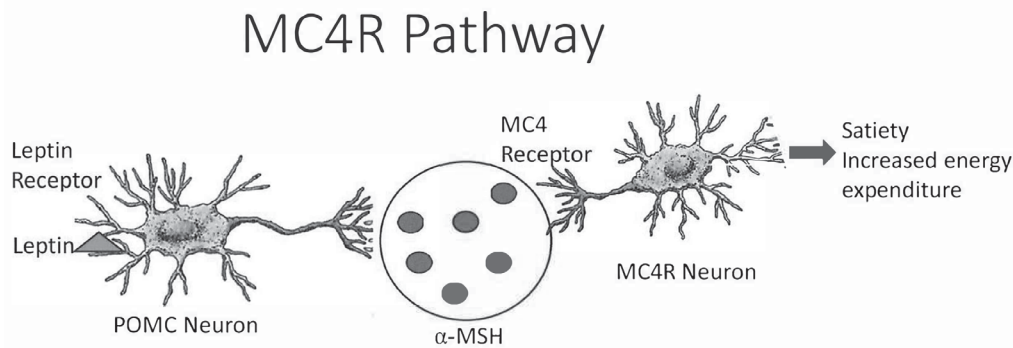
Hyperphagia is associated with rare obesity-related diseases and presents as a pathologic, insatiable hunger accompanied by abnormal food-seeking behaviors. Although there is no universally accepted definition of hyperphagia, most physicians will say that “you know it when you see it.” Expert groups define hyperphagia as “having prolonged time to satiation when eating, shortened duration of satiety following a meal, prolonged feelings of hunger, and a persistent preoccupation with food, which leads to food-seeking behaviors.”³ Hyperphagia is extremely difficult to manage, and patients and their families report that hyperphagia negatively affects many aspects of their lives, including sleep, emotional regulation, ability to work, participation in activities outside of the home, and relationships with family and friends.³

Hyperphagia caused by rare obesity syndromes is thought to be due to dysfunction of certain areas of the hypothalamus. Understanding the biology of this condition has evolved through research on hyperphagia in PWS and in genetic conditions that affect the melanocortin-4 receptor (MC4R) pathway, as well as on hyperphagia associated with damage to the MC4R pathway (eg, craniopharyngioma or other brain tumors/injuries). Within the nuclei of the hypothalamus lie key receptors for satiety-promoting gut hormones, as well as appetite and satiety signaling

pathways, such as the leptin–MC4R pathway. Research indicates that the MC4R pathway is critical to the presence or absence of hyperphagia in these rare diseases associated with hypothalamic obesity.^{3–5} The MC4R pathway regulates energy balance, appetite, and food intake by controlling metabolic rate, caloric expenditure, and the hunger drive.^{3–5} Disruptions in this signaling can occur with genetic disorders or be secondary to acquired hypothalamic damage, both of which frequently lead to hyperphagia, which, along with decreased energy expenditure, worsens obesity and negatively affects quality of life. Individuals with PWS are thought to have changes in the gene expression of receptors along this pathway, thereby interfering with the MC4R pathway's natural physiologic role and resulting in hyperphagia.⁶ Advancements in knowledge about the pathophysiology causing hyperphagia, combined with increased availability and affordability of genetic testing, emphasize the need for a standardized definition of hyperphagia that can distinguish it from other overeating disorders to support improved diagnosis and management of affected patients. Providers who manage patients with hyperphagia know that it is very different from just excessive appetite, and it is critical that insurance companies cover any current and future medications to treat this debilitating condition.

Physiologically, when the hypothalamus is functioning correctly, upstream activation of MC4R by release of α -/ β -melanocyte-stimulating hormone (α -/ β -MSH) from hypothalamic pro-opiomelanocortin (POMC)-expressing neurons decreases food intake and increases energy expenditure.^{4,5} Increased appetite is typically activated by inhibition of MC4R by agouti-related peptide (AgRP), an inverse agonist, released by hypothalamic AgRP-expressing neurons.^{4,5,7} Deficiencies in upstream generation of α -/ β -MSH can occur through a variety of mechanisms, including variants in genes involved in the MC4R pathway, such as the leptin receptor gene (*LEPR*) or POMC gene (*POMC*), which are signals required to activate the MC4R pathway (*Figure 1, following page*). Additionally, stimulation of

Figure 1. Melanocortin-4-Receptor Pathway



[Color—Print (Color Gallery page CG19) or web & ePub editions]

serotonin receptor 2C expression in POMC neurons can enhance α -MSH expression and suppress AgRP activity on MC4R receptors (AgRP inhibits the MC4R pathway, resulting in increased hunger).^{7,8} Thus, genetic alterations that affect the serotonin receptor 2C can further dysregulate the MC4R signaling pathway. In PWS, the serotonin receptor 2C is thought to be abnormal due to loss of paternal expression of *SNORD116* associated with the genetic etiology of PWS.⁹

Impairments in the MC4R pathway ultimately result in hyperleptinemia and hyperinsulinemia, which facilitate hyperphagia and increased energy intake. This is exemplified in PWS, as affected individuals have increased insulin sensitivity, which, in the context of hyperinsulinemia, leads to increased fat mass and, in turn, elevated circulating leptin levels, inducing central insulin and leptin resistance and subsequently leading to obesity and hyperphagia.¹⁰ Abnormal development of the hypothalamus, along with decreased insulin receptors and abnormalities in both the MC4R pathway and serotonin receptor 2C expression, likely underlie severe hyperphagia seen in individuals with PWS.^{9,10} Due to this constellation of conditions that contribute to hyperphagia in PWS, affected individuals also often experience extreme anxiety around food and may have tantrums and outbursts related to food (especially during attempts at food restriction).

Variations in the underlying pathophysiology and resulting impairment of the MC4R pathway

signaling influence the severity of hyperphagic symptoms and behaviors.¹¹ Genetic conditions that cause hyperphagia can be associated with differing severity of functional effects on MC4R signaling.^{10,11} Additionally, the presentation of hyperphagia can be confounded by neurocognitive impairment in individuals with certain genetic conditions.^{7,11} Thus, the presentation of hyperphagia is variable, even within the same genetic condition.

Clinical Case Vignettes

Case 1

An 18-year-old man with PWS is accompanied by his parents for a follow-up appointment. He was diagnosed with PWS (due to a 6 megabase deletion) at age 3 weeks. His clinical course has followed the classic nutritional phases of appetite in PWS, with initial failure to thrive in infancy/G-tube feeding until 6 months of age (phase 1a), normal appetite/weight until 18 months of age (phase 1b), followed by weight gain despite no change in caloric intake (phase 2a). At age 5, he developed an increased interest in and awareness of food, along with continued excessive weight gain (phase 2b). At age 12, his parents discovered hidden food wrappers and stolen money in the back of his closet. He ultimately admitted that he was constantly thinking about food and taking either money or food whenever he could (phase 3). He developed prediabetes with a hemoglobin

A_{1c} value of 6.1% (43 mmol/mol). His current treatment regimen consists of GH, levothyroxine, testosterone cypionate, and metformin, 1000 mg daily. His weight had increased by 11.2 lb (5.1 kg) over the previous 3 months. The refrigerator and cabinets are locked at home. He is on an 800-calorie-per-day diet but is still gaining weight. His parents inquire about clinical trials or treatment options.

Which of the following is the best next step in this patient's care?

- A. Contact the department of children and family services to report neglect
- B. Increase the metformin dosage to 2000 mg daily
- C. Start a GLP-1 receptor agonist
- D. Start DCCR therapy
- E. Provide intensive dietary intervention to implement a dietary regimen that will help with weight control and diabetes management

Answer: E) Provide intensive dietary intervention to implement a dietary regimen that will help with weight control and diabetes management

Extensive diet counseling was provided to help implement a well-balanced diet excluding sweet-tasting foods or drinks (Answer E) before considering possible treatment with DCCR, which has been FDA approved to treat hyperphagia in PWS.¹²⁻¹⁴ Given the patient's obesity, ongoing weight gain, and prediabetes, the most significant concern with starting this medication is the potential development of type 2 diabetes. Dietary changes and weight loss are essential before starting a medication for hyperphagia.

Case 1, Continued

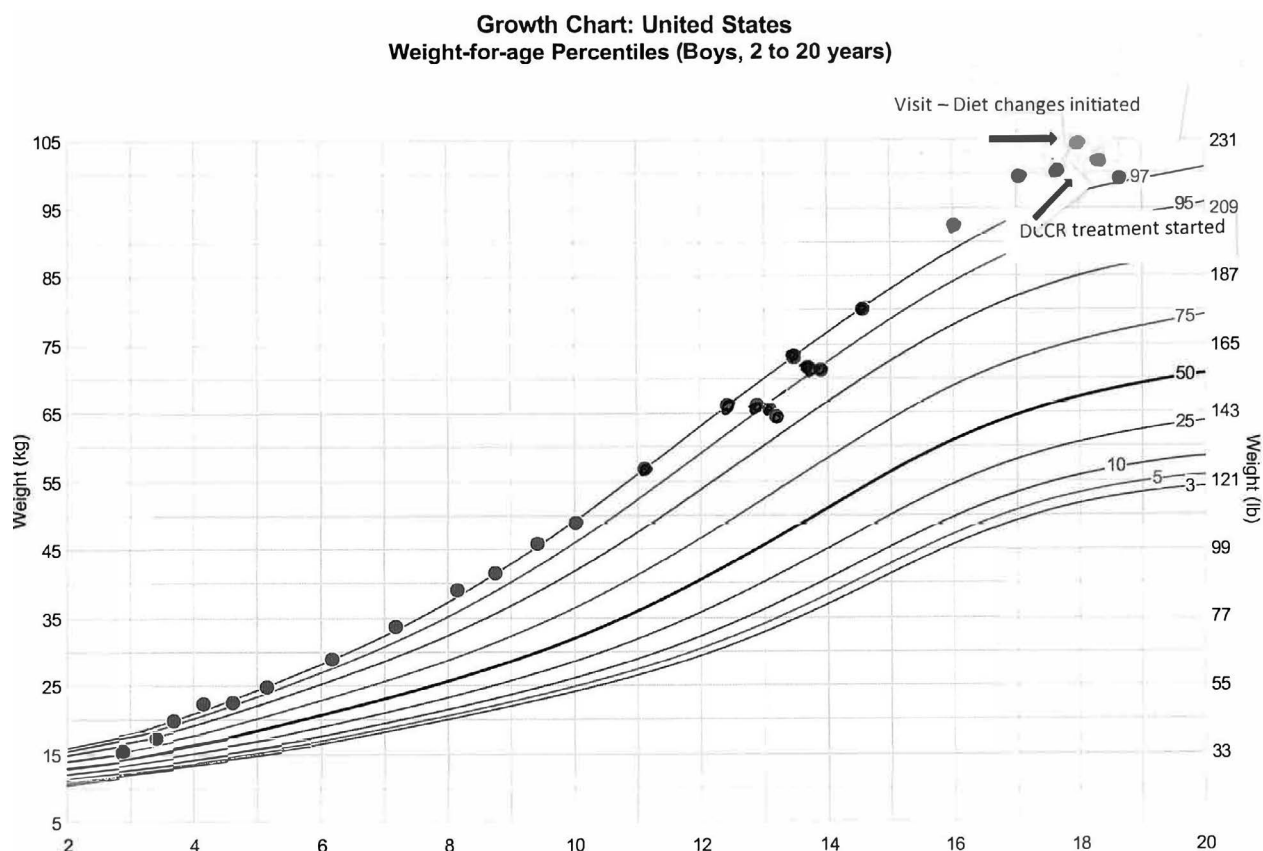
After the family adopted dietary and exercise changes, as evidenced by a 4.4-lb (2-kg) weight loss in 3 months (the first time the patient had ever experienced a decline in his weight), DCCR was initiated to treat hyperphagia. DCCR was FDA approved for the treatment of hyperphagia in the

United States in March 2025. DCCR agonizes the K_{ATP} channels, which typically hyperpolarize the cell membrane. The most well-known action of DCCR is to agonize the K_{ATP} channel in β cells, which reduces hyperinsulinemia and its contribution to fat deposition, insulin resistance, and increased leptin secretion by adipose tissue.¹⁵ Additionally, DCCR hyperpolarizes the K_{ATP} channel in neuropeptide Y (NPY)/AgRP/gamma-aminobutyric acid (GABA) neurons, which decreases the secretion of NPY and AgRP, 2 potent appetite-stimulatory neuropeptides balancing orexigenic and anorexigenic signaling.¹⁵ Additionally, DCCR is hypothesized to inhibit GABA release, thereby reducing hyperphagia.¹⁵ DCCR is thought to agonize the K_{ATP} channel in the dorsal motor nucleus of the vagus, part of the dorsal vagus complex, thus increasing satiety, reducing hyperinsulinemia, and improving leptin and insulin sensitivity.¹⁵ Within the adipocytes, DCCR increases β -oxidation of fat and reduces de novo synthesis of triglycerides, thereby reducing fat mass.¹⁵

In this patient, the DCCR dosage was titrated to 4 mg/kg per day over 6 weeks. Fasting blood glucose was monitored weekly during the first 3 months of therapy, and the patient was seen for follow-up evaluation and laboratory monitoring. After 3 months of therapy, his weight decreased by 11 lb (5 kg) (*Figure 2, following page*), and his hemoglobin A_{1c} decreased to 5.7% (39 mmol/mol). His parents reported a reduction in his interest in and awareness of food. He was asking significantly fewer food-related questions, was able to go without snacks some days (which was unheard of for many years), and often brought home part of his lunch uneaten. Additionally, his overall behaviors improved with fewer food-related meltdowns and less repetitive talking. Hypertrichosis was the only adverse effect of the medication.

This case emphasizes the need for dietary modification in addition to medication therapy for the treatment of obesity and hyperphagia. Medication alone may provide some benefit, but when combined with dietary and exercise changes, it can achieve true, long-term efficacy in treating hyperphagia and obesity. The patient has

Figure 2. Patient's Growth Curve Before and After Diet Changes and DCCR



continued to lose weight on this regimen, and his hyperphagia has improved to the point that he no longer requires constant 1:1 supervision at school and home to prevent food sneaking.

Case 2

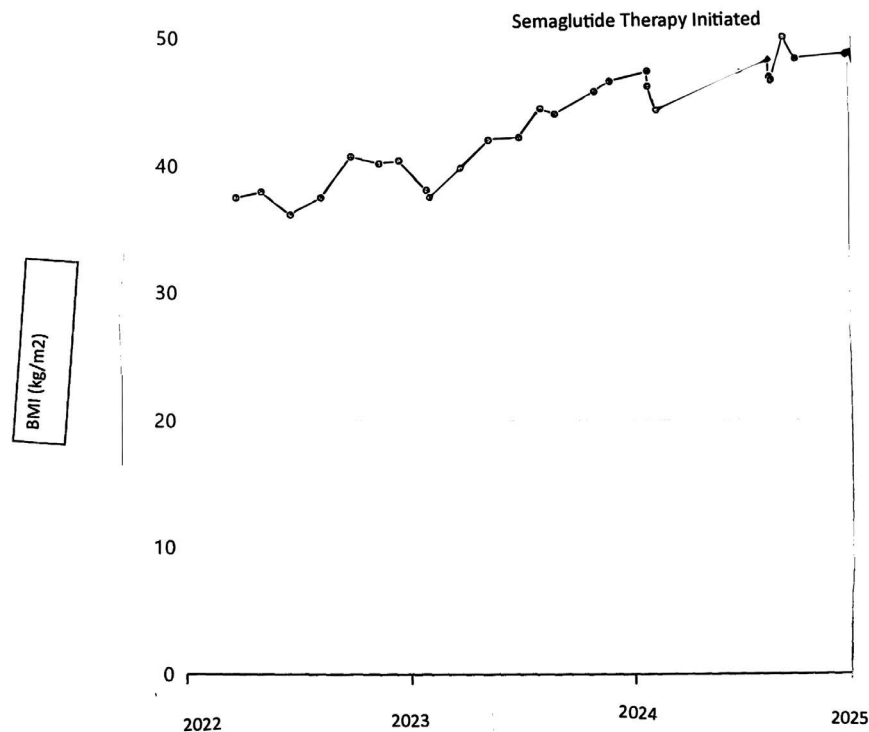
A 16-year-old girl with PWS (due to uniparental disomy) is followed by psychiatry every 3 months. She has not taken GH since age 14. Current medications are levothyroxine, estradiol, progesterone, metformin twice daily, risperidone twice daily for behavioral problems, fluoxetine for obsessive-compulsive behaviors, guanfacine for impulsive behaviors, and methylphenidate for excessive daytime sleepiness (sleepiness started after initiating guanfacine and risperidone). Her BMI is 54 kg/m². She is asleep during the visit. Her parents report that she refuses to wear continuous positive airway pressure (CPAP) at night, and her breathing often pauses during sleep. All food is

locked at home. The patient is currently not in school because she was expelled for behavioral problems, and both parents work, so she is home alone during the day. She is not physically active. She has skin-picked lesions on her arms and legs, several of which have been open for longer than 2 months. She has grade 2 hypertension, mixed hyperlipidemia, and a hemoglobin A_{1c} value of 10.2% (88 mmol/mol).

Which of the following is the best next step in this patient's management?

- Intensive dietary counseling with calorie restriction
- Start DCCR
- Start a GLP-1 receptor agonist
- Refer back to pulmonology to get psychology involved to improve adherence to CPAP
- Contact the department of children and family services to report medical neglect

Figure 3. Patient's BMI Before and After Treatment With a GLP-1 Receptor Agonist

**Answer: C) Start a GLP-1 receptor agonist**

This patient's treating psychiatrist started DCCR to ameliorate hyperphagia, but the patient developed worsening shortness of breath, oxygen saturation of 85%, and pulmonary edema. Patients with longstanding, untreated obstructive sleep apnea and resulting pulmonary hypertension or right heart failure are at high risk for developing pulmonary edema with DCCR therapy. Therefore, initiating DCCR is not recommended for these patients or for those with significantly elevated hemoglobin A_{1c} levels until weight loss or treatment of comorbid conditions has been addressed.

The correct first-line treatment in this case is a GLP-1 receptor agonist to treat type 2 diabetes. The patient's BMI before and after treatment with a GLP-1 receptor agonist is shown in *Figure 3*. Studies of GLP-1 receptor agonists in patients with hypothalamic obesity, including PWS, have also shown success in treating type 2 diabetes, as in the general population, but have mixed results for treating obesity and hyperphagia,^{16,17} with

no long-term improvements in weight in these populations.

Case 3

A 27-year-old woman with panhypopituitarism and hypothalamic obesity presents for annual endocrine evaluation. She has had obesity since age 9 months and was voraciously hungry, even as a newborn. She has required emergency involuntary psychiatric hospitalization 3 times in adolescence and young adulthood for threatening to kill her parents to get to food. Her parents have all food locked at home and sleep in front of the kitchen to prevent her from accessing food during the night. Current medications are GH therapy, levothyroxine, liothyronine, estrogen/progesterone, hydrocortisone, and DDAVP. Her weight has increased by 22 lb (10 kg) over the past year (BMI = 53.28 kg/m²), despite her report of following a low-calorie diet and walking her dog for exercise. She has obstructive sleep apnea but is unable to tolerate CPAP therapy. She is

married, has no children, and is unable to maintain a job after being fired several times for stealing food. She reports depression due to her medical conditions and requests any possible treatment for hyperphagia and obesity.

Which of the following is the best next step in this patient's treatment?

- A. Adjust hydrocortisone and thyroid hormone replacement dosages
- B. Refer to psychiatry for treatment of depression

- C. Refer for more advanced therapy for obstructive sleep apnea
- D. Perform a complete genetic workup to evaluate the cause of panhypopituitarism and hypothalamic obesity
- E. Refer to bariatric surgery for consideration of gastric bypass or sleeve gastrectomy

Answer: D) Perform a complete genetic workup to evaluate the cause of panhypopituitarism and hypothalamic obesity

Figure 4. Patient's Genetic Test Results Reporting a Pathogenic Variant in the LEPR Gene

Exome w/CNV Evaluation, Proband																	
Clinician Provided Information																	
Indication for testing: Early-onset morbid obesity, hyperphagia, short stature, intellectual disability, and Prader-Willi-like features.																	
Family history: Maternal and paternal histories were not reported. This individual is of Puerto Rican descent.																	
Secondary findings status: Opt-in																	
Summary																	
POSITIVE WITH ADDITIONAL FINDING IDENTIFIED																	
ALTERATION(S) WITH CLINICAL RELEVANCE DETECTED																	
Results																	
Primary Interpretation																	
Exome sequencing was performed, including copy number variant (CNV) analysis and mitochondrial genome sequencing. This test identified a homozygous pathogenic variant in the LEPR gene. Pathogenic biallelic variation in LEPR is associated with morbid obesity due to leptin receptor deficiency (OMIM #614963), which can present with early-onset obesity, hyperphagia, frequent infections, and hypogonadotropic hypogonadism (PMID: 17229951, 27313173). A homozygous variant of uncertain significance was identified in the HERC2 gene. Pathogenic biallelic variation in HERC2 is associated with HERC2-associated intellectual disability (OMIM #615516), which has been reported to cause global developmental delay, intellectual disability, and hypotonia (PMID: 23243086, 23065719). In addition, a pathogenic variant in TTR was identified, which is associated with familial transthyretin amyloidosis (OMIM #105210), and it is unclear if this variant is contributing to the phenotypic presentation of the current individual. Please see the additional and secondary findings section of this report for more information on the variant identified. This test was ordered as a proband only. No other familial sample was used in the interpretation of this test result. This test did not identify secondary findings as defined by the American College of Medical Genetics and Genomics (ACMG) published guidelines (PMID 27854360).																	
Primary Results																	
<table border="1"> <thead> <tr> <th>Gene</th><th>Variant/Zygosity</th><th>Clinical Relevance</th><th>Inheritance</th><th>Associated Phenotype</th><th>Reference Sequence</th></tr> </thead> <tbody> <tr> <td>LEPR</td><td>c.93G>A (p.Trp31*) / Homozygous</td><td>Pathogenic</td><td>Autosomal Recessive, Unknown Familial Inheritance</td><td>Morbid obesity due to leptin receptor deficiency</td><td>NM_002803.5</td></tr> </tbody> </table>						Gene	Variant/Zygosity	Clinical Relevance	Inheritance	Associated Phenotype	Reference Sequence	LEPR	c.93G>A (p.Trp31*) / Homozygous	Pathogenic	Autosomal Recessive, Unknown Familial Inheritance	Morbid obesity due to leptin receptor deficiency	NM_002803.5
Gene	Variant/Zygosity	Clinical Relevance	Inheritance	Associated Phenotype	Reference Sequence												
LEPR	c.93G>A (p.Trp31*) / Homozygous	Pathogenic	Autosomal Recessive, Unknown Familial Inheritance	Morbid obesity due to leptin receptor deficiency	NM_002803.5												

This patient underwent genetic evaluation as part of an initiative to diagnose genetic causes of hyperphagia and obesity.^{18,19} A pathogenic variant was identified in the gene encoding the leptin receptor (*Figure 4, preceding page*), and setmelanotide therapy was initiated. Setmelanotide is FDA approved to treat this condition and has shown long-term successful weight control.^{20,21}

Key Learning Points

- Hyperphagia and hypothalamic obesity are difficult to manage and negatively affect the quality of life of patients and their family members.
- Despite the complex nature of these conditions, some effective treatments are available. Medications for hyperphagia can have adverse effects and are not safe or effective for every patient affected by hyperphagia and obesity. However, they can be life-changing for many people.
- Diet must be an integral component of any medical intervention for individuals with hyperphagia. Optimizing diet can help manage weight and enhance the efficacy of medications.

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Pituitary Tumor Survivorship: Transitioning From Pediatric to Adult Endocrine Care

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Discuss knowledge gaps and obstacles of transitioning adolescents with pituitary tumors to adult endocrine care services.
- Describe the dynamic changes of pituitary hormones during the transition years and how endocrinopathies can be managed during and after transition to adult endocrine care.
- Describe the possible outcomes after transition and develop management strategies in childhood and adolescence to optimize physiological outcomes in adulthood.
- Acknowledge the importance of a multidisciplinary team approach in optimizing the management of pituitary tumors and their clinical sequelae after transition into adulthood.

Significance of the Clinical Problem

Transition refers to the structured process that ensures continuity of health care for adolescents with complex chronic medical conditions as they move from pediatric to adult health services. The complexity of this process is well recognized, including the lack of standardized diagnostic criteria, high treatment costs, and

limited experience among clinicians managing rare pituitary tumors. Managing patients in transition requires periodic testing to reassess hormonal status and ongoing monitoring of signs and symptoms to guide hormonal dosage adjustments. Individualized treatment planning is essential, as some adult patients might benefit more from hormone replacement than others, whereas others, such as those with idiopathic GH deficiency (GHD), may experience recovery of endogenous GH secretion by the time adult height is achieved and therefore, can experience adverse effects if treated with GH when not indicated.¹ Despite awareness of this issue, the need remains to improve this process in real-world practice.

Transition age marks the period between the end of puberty and the attainment of peak bone mass.² It is a time of physical changes, including growth and sexual maturation, as well as pronounced cognitive and emotional development. Young people begin to navigate adult relationships, employment, tertiary education, independent living, and a social life, which may include alcohol and recreational drugs. This is a complex stage of life that can be difficult even for healthy individuals, and even more so for patients with chronic medical conditions.

Pituitary tumors are rare in children and adolescents, especially before puberty, and are generally more aggressive, treatment-resistant, or part of a genetic syndrome. These tumors are characterized in the same way as in adults: nonfunctioning (eg, craniopharyngioma and

nonfunctioning pituitary adenomas [NFPAs]) or functioning (eg, prolactinomas, Cushing disease, somatotropinomas, and, rarely, TSHomas). Typical endocrine sequelae in pituitary tumor survivors include persistence or recurrence of functioning pituitary tumors and/or hypopituitarism.³ During the transition period, special attention should be directed to growth, puberty, fertility, and lifestyle. Currently, no specific studies exist on optimizing care when transitioning the care of pituitary tumor survivors. Existing transition processes are adapted from models used for other chronic childhood-onset diseases (eg, diabetes and cystic fibrosis).⁴⁻⁶ Given the variability in patient readiness, cognitive function, comorbidities, health care access, insurance coverage, and availability of local expertise, transitioning the care of pituitary tumor survivors requires an individualized, multidisciplinary approach. Close collaboration between pediatric and adult endocrinologists is essential to ensure a seamless, effective transition of clinical care.⁷

Practice Gaps

- Despite the availability of clinical guidelines providing a framework for the transition of care for young adults with several chronic childhood-onset diseases, there remains uncertainty and variation in the approach to transitioning the care of pituitary tumor survivors to adult endocrine care services.
- Transitioning pediatric patients with varying levels of readiness, cognitive abilities, coexisting comorbidities, and health care access creates significant challenges in moving them successfully to adult endocrine care services.
- Lack of standardized diagnostic criteria, cost of treatment, and unfamiliarity or inexperience of pediatric and adult clinicians treating rare and subtle forms of childhood-onset pituitary disorders compound the challenges in successfully transitioning the care of pituitary tumor survivors.
- Patients with pituitary tumor disorders at risk of evolving pituitary endocrinopathies may not have been diagnosed or may have had suboptimal biochemical confirmation and resultant inappropriate treatment that could lead to later comorbidities.

Discussion

In pediatric care, medical responsibility is largely shared between the physician and the family; however, as these patients transition into adulthood, they are expected to assume ownership of their own health care.⁸ Adequate preparation for adult-oriented care can reduce loss to follow-up and lower the risk of developing complications and comorbidities in adulthood.⁸ Structured transition models have been developed to facilitate the successful transfer of care, but none are specifically tailored for pituitary tumor survivors. The transition process is recommended to start in early adolescence (age 12) and should address 6 core elements: development of a transition policy or guide (ages 12-14), patient tracking and monitoring (ages 14-18), assessment of transition readiness (ages 14-18), transition planning (ages 14-18), transfer of care (ages 18-21), and confirmation of transition completion (ages 18-23).⁹ In the United Kingdom, the National Health Service has implemented the *Ready Steady Go* program, a flexible transition framework applicable across medical subspecialties. Under this model, transition begins at age 11 to 12 years, and progress is evaluated at each stage using structured questionnaires. In the final phase, termed *Hello*, the patient is formally transferred to adult care services.¹⁰ Throughout the transition period, pediatric and adult care teams conduct joint meetings and shared clinical visits to review patient histories and align treatment plans.

Pituitary tumor survivors are particularly vulnerable during the transition period due to disease complexity, the need for lifelong endocrine surveillance, and the risk of late complications. Effective transition care requires early planning and a coordinated, multidisciplinary approach.

Progressive engagement of adolescents in their own care enhances self-management skills, autonomy, and adherence. Equally important is a pathway for structured communication between pediatric and adult providers, including formal handovers, shared medical records, and joint transition clinics. Continuing education for clinicians is essential, particularly in adult settings where clinical experience with rare pediatric-onset pituitary disorders may be limited. Improving access to specialized endocrine care through streamlined referral pathways, multidisciplinary services, and telemedicine may reduce loss to follow-up. Consensus-based recommendations, supported by longitudinal studies and multicenter registries, are needed to standardize care. Tailored strategies are required for vulnerable subgroups, including patients with cognitive, psychosocial, or socioeconomic challenges, to ensure equitable and sustainable engagement in adult health care services.

For pituitary tumor survivors, transition offers an opportune time to reevaluate endocrinopathies, as changes in anterior pituitary function are well described and new deficits and comorbidities may develop or evolve. For example, between 25% and 88% of patients can recover their GH secretion at the time of transition.¹¹ Additionally, the primary physiological change during transition is puberty with resultant development of secondary sexual characteristics, pubertal growth spurt with fusion of the growth plates to achieve adult height, and maturation of gonads for sperm and egg production. Depending on the severity of hypopituitarism, the clinician must manage the replacement of one or multiple pituitary hormone deficiencies during this time. At the age when most adolescents are considered for transition to adult care, most patients have achieved final adult height and completed puberty. Thus, the ensuing discussion with the patient should focus on the physiological transitions of each pituitary hormone after pubertal completion and attainment of adult height.

Nonfunctioning Pituitary Adenomas

NFPAs account for less than 10% to 15% of all pediatric pituitary tumors, and most are typically diagnosed after age 16 years.¹² Genetic screening is indicated, as NFPAs may be associated with *MEN1* or *AIP* pathogenic variants. Symptoms are related to mass effects of macroadenomas (eg, headache, visual field defects, or signs of hypopituitarism),¹³ while microadenomas are often found incidentally.¹⁴ When diagnosed after puberty, management of these tumors is similar to that in adults. Surgery is the treatment of choice for symptomatic NFPAs and for tumors growing over time. A second surgery and/or radiotherapy may be considered and discussed within a multidisciplinary team. As in adults, long-term MRI surveillance is recommended for pediatric patients with macroadenomas, with an individualized surveillance strategy based on the tumor's clinicopathological grade at surgery, location, lesion size, and estimated growth rate.

Hypopituitarism

The mainstay of medical treatment in patients with hypopituitarism is replacement of the appropriate hormones.

Growth Hormone

While statural growth may have completed during the transition period, somatic development continues, progressing towards peak bone mass.¹⁵ Upon discontinuation of GH treatment during the transition period, abnormal body composition and unfavorable shifts in cardiovascular risk markers have been reported.¹⁶ Cessation of GH upon linear growth completion may also limit peak bone mass attainment, increasing the susceptibility to bone mineral density deficits in adult life. The subsequent development of osteoporosis and the associated risk of fragility fractures are partly contingent on the peak bone mass achieved during adolescence.¹⁷ After GH discontinuation during transition, negative effects on quality of life and psychological well-being have also been reported.¹⁸

Continued GH treatment in patients beyond linear growth achievement results in increased bone mineral density and lean body mass, and improved quality of life compared with cohorts with GH deficiency (GHD) not receiving ongoing GH replacement.¹⁹ In accordance with current guidelines,²⁰ individuals with persistent GHD should maintain GH replacement therapy throughout transition, aiming for complete skeletal maturation and optimization of metabolic profile. However, adolescents may perceive the end of growth as an opportunity to discontinue GH treatment. Recent availability of once-weekly, long-acting GH formulations may help patients to consider resuming GH treatment in the transition period.

Additionally, transition care can be further complicated for cancer survivors with acquired GHD, considering requirements related to oncology care and the range of possible comorbidities with their primary diagnosis. For these patients, effective transition from the pediatric to the adult endocrinologist requires diligent referral pathways, including from the pediatric oncologist to the pediatric endocrinologist, and from the pediatric endocrinologist (and likely adult oncologist) to the adult endocrinologist with expertise in managing adults with GHD and, more generally, a collaborative approach with open lines of communication among members of the multidisciplinary team.²¹

GH replacement should be considered only for patients with confirmed persistent GHD during the transition period. Between 30% and 50% of children diagnosed with idiopathic GHD have normal GH secretion when retested with GH-stimulation testing.²² Reevaluation of the GH axis is recommended for patients with GHD plus 2 or fewer of the following: other pituitary hormone deficiency, idiopathic isolated GHD (with or without minor pituitary/ectopic posterior pituitary anomalies), and history of cranial irradiation. Retesting patients with childhood-onset GHD is recommended after linear growth has ceased (growth velocity <1.5-2 cm/y) to identify those who genuinely require long-term

GH therapy. Any retesting must be performed at least 1 month after GH is discontinued in the transition period.²⁰ Current guidelines exempt retesting patients with ³³ pituitary hormone deficiencies and low IGF-1, documented transcription factor pathogenic variants, isolated GHD linked to identified pathogenic variants, or specific pituitary/hypothalamic structural defects (excluding ectopic posterior pituitary).²⁰

Recommended GH-stimulation tests include the insulin tolerance test (ITT), glucagon, macimorelin, and GHRH-arginine tests.¹² Different GH cut-points for the ITT have been proposed, including <5 ng/mL (<5 µg/L),²⁰ <6.1 ng/mL (<6.1 µg/L),²³ or <5.6 ng/mL (<5.6 µg/L).²⁴ If the ITT is contraindicated (eg, seizure disorders), macimorelin (GH cut-point ≤2.8 ng/mL [2.8 µg/L])²⁰ and glucagon (GH cut-point ≤5.8 ng/mL [5.8 µg/L])²⁵ tests are acceptable alternatives, although normative values for this age group are not well-defined. The GH cut-points for the GHRH/arginine test are BMI-dependent; however, this test is not advised for idiopathic GHD or for those with a history of cranial irradiation due to potential false-negative results.²⁰ Notably, macimorelin and GHRH analogues are currently unavailable in the United States.

Regarding recommencing GH treatment, current Endocrine Society guidelines recommend higher starting GH doses for patients younger than 30 years (0.4 to 0.5 mg daily) than for older adults,²⁶ whereas the American Association of Clinical Endocrinology clinical practice guidelines recommend starting at 50% of the previous pediatric dose.²⁰ When adjusting GH doses, they should be tailored based on age and gender-adjusted IGF-1 levels, estrogen status, clinical response, and absence of adverse effects, with the goal of normalizing IGF-1. For adolescents with GHD, correct timing and gradual increase of sex hormone replacement is crucial for achieving optimal final height and aligning their pubertal development (menarche or virilization) with that of their peers.²⁷ This treatment must be individualized to avoid compromising final height from too-early initiation.

Treatment with GH is generally safe. Previous studies indicate that GH therapy does not increase the risk of secondary cancers in childhood cancer survivors,²⁸ and an increased risk of meningiomas was linked to radiotherapy, not to GH treatment.²⁹ Sustained GH replacement therapy during transition care optimizes the chances to maintain proper metabolic, cardiovascular, and physical health, in addition to providing psychological benefits and improved quality of life during adulthood.

Gonadal Steroids

Pituitary tumors can cause acquired hypogonadotropic hypogonadism (HH) in the transition age. If due to a prolactinoma, HH is treated medically, while surgery is the first-line treatment for other functioning tumors. Treatment goals for HH include developing sexual characteristics, normalizing growth, ensuring continued bone health, normalizing body composition, and inducing gonadal maturation for future fertility. There is a subset of patients diagnosed with idiopathic HH who may later undergo reversal, resulting in hypothalamic-pituitary-adrenal axis activation with normalization of gametogenesis associated with steroidogenesis. Therefore, patients with idiopathic HH require lifelong monitoring for such reversal, and if it occurs, monitoring for future relapses will need to be addressed.

Notably, testosterone therapy does not lead to testicular growth or spermatogenesis in men; thus, induction of fertility requires treatment with either pulsatile GnRH or exogenous gonadotropins. Several regimens have been published, differing based on the indication for treatment and severity of hypogonadism. One regimen involves hCG, 500 to 3000 IU twice weekly, increased to every 2 days, with the dose adjusted based on serum testosterone levels, and recombinant FSH, 75 to 225 IU 2 to 3 times weekly.³⁰ In men, testosterone levels are a reliable biomarker of dosing, but the same is not true of estrogen levels in women. In women, ovulation and pregnancy can be achieved by pulsatile GnRH administration or gonadotropin combination therapy. Estrogen

therapy should be initiated at a low dosage (15% to 25% of the adult dosage) and increased gradually every 4 to 6 months.³¹ One dosage regimen that can be considered is a patch containing 25 mcg of 17 β -estradiol/24 hours, cut into 4 equal-sized pieces: 1 piece is applied on the skin before going to bed and is removed in the morning. After 4 to 6 months, the dosage can be increased to 2 pieces at night, with 1 piece being removed the following morning and the other remaining on the skin during the day. The dosage is usually increased approximately every 4 to 6 months to 1 patch of 25 to 100 mcg and is changed twice weekly. Otherwise, oral 17 β -estradiol may be taken 0.5 mg every day or every second day as an initial dosage, increasing gradually.³¹ The objective is to develop secondary sexual characteristics over 2 to 3 years. When “breakthrough” bleeding occurs, progesterone treatment (eg, 5 mg medroxyprogesterone acetate daily for 10 days every 4-5 weeks) should be initiated to prevent endometrial hypertrophy.³¹ Response to therapy can be monitored by evaluating for the development of secondary sexual characteristics, bone maturation, and uterine volume.

Fertility and reproductive considerations should be delineated during the transition period and continuously adapted to the patient’s maturity and needs. In HH, induction of gonadotropin secretion by pulsatile GnRH or continuous gonadotropin administration may improve folliculogenesis and ovulation, thereby improving fertility rates. To promote follicular growth and maturation, exogenous gonadotropins (eg, human menopausal gonadotropin or a combination of recombinant LH and FSH) are administered, followed by an hCG injection. The possibility of unwanted pregnancy and contraception should also be discussed openly. Each treatment option must be tailored to the patient’s needs and preferences.

Thyroid

Thyroid hormones are crucial for normal growth and neurodevelopment; for regulating basal metabolic rate, body temperature, heart rate, and cardiac output; and for promoting gastrointestinal

motility and renal clearance of salt and water. However, signs and symptoms of hypothyroidism can be subtle and nonspecific. Diagnosis is based on serum TSH and free T_4 levels, and levothyroxine is the treatment of choice to restore euthyroidism, based on free T_4 , not TSH, levels. In females on estrogen-containing contraceptive pills and in women who are pregnant, the dosage of levothyroxine needs to be increased. New formulations of levothyroxine are now available in some countries for patients who cannot swallow tablets, such as a liquid solution and a softgel capsule. Combination treatment with liothyronine and levothyroxine has been used, but its efficacy is mixed compared with levothyroxine monotherapy.³² If ACTH deficiency is also present, then glucocorticoid (GC) replacement therapy should be started before levothyroxine to avoid precipitating adrenal crisis. If the patient is also on GH therapy, higher dosages of levothyroxine are needed, as GH can decrease T_4 and increase T_3 levels.²⁰

Adrenal

Mild cases of central adrenal insufficiency can be asymptomatic. If undetected, patients can present with an adrenal crisis during times of stress, trauma, surgery, or illness. In adolescents with central adrenal insufficiency, hydrocortisone is the GC of choice because of its immediate efficacy and short duration of action, which facilitates dose titration, and a lesser effect on linear growth compared with longer-acting GCs.³³ Hydrocortisone can be given thrice or twice daily, depending on adherence, with the highest dose in the morning, on waking, and the last dose no later than 18:00 hours. Long-acting GCs (eg, prednisone or prednisolone) may be considered in patients who cannot adhere to a multidose daily regimen; however, dexamethasone should be avoided as it can slow growth. Two modified-release hydrocortisone formulations have been studied, but are not currently available in the United States.

Prevention of adrenal crisis should consider predicting precipitating risk factors, including infections, surgical procedures, physical or

psychological stress, or sudden GC interruptions. Adrenal crisis is prevented by increasing the GC doses and by avoiding immediate cessation of GC therapy. Patient education plays a crucial role in recognizing when to stress-dose and when parenteral hydrocortisone is required. Adolescence presents a particularly problematic time, as patients may be moving from childhood and parental dependence to a new sense of independence and leaving home. Adherence tends to be more variable; they may start drinking alcohol and taking other stimulants, and they might postpone the afternoon hydrocortisone dose if they have bizarre sleeping habits. Conversely, GC overreplacement exacerbates the metabolic syndrome, cardiovascular disease, and bone disease. GC treatment represents a life-saving therapy, and education is essential to protect patients from adrenal crisis. Notably, GC requirements should be tailored to the patient's lifestyle.

Arginine Vasopressin

Although arginine vasopressin (AVP) deficiency may have been well-managed for years, during the transition period, young patients may attempt to “normalize” fluid intake in circumstances of perceived need. Hence, patient continuing education is essential. Desmopressin, preferably administered orally, is the treatment of choice. Desmopressin is also available as an intranasal spray and parenteral formulation. While monitoring AVP deficiency, it is crucial to monitor serum sodium levels and fluid input and urine output, which will typically indicate overtreatment or undertreatment with desmopressin. Adipsic AVP deficiency is a rare yet challenging complication associated with high morbidity and mortality. Clinicians, health care workers, and families should supervise fluid and desmopressin intake, with fixed regimens of fluid throughput, weight assessment, and fluid output measurements.³⁴

When managing AVP deficiency, it is important to evaluate whether a patient on desmopressin should also be on GC replacement therapy. Adrenal insufficiency can lead to hyponatremia, which may be exacerbated by desmopressin administration. Adolescents with hypothalamic-pituitary diseases are often taking

GCs and desmopressin simultaneously; therefore, clinicians and patients should be aware of the need to increase their GC dosages and check their electrolytes before further desmopressin administration to prevent hyponatremia from developing.³⁵ Excessive beer binge drinking and certain recreational drugs, such as MDMA (“ecstasy”), that lead to overdrinking may be dangerous while on desmopressin. Adolescents should be educated on desmopressin dose adjustments to allow their thirst to guide their fluid intake, and to reevaluate their desmopressin dosages when they use the restroom frequently and/or become very thirsty. If managed appropriately, desmopressin is generally safe and effective in the treatment of AVP deficiency.

Functioning Pituitary Tumors

Prolactinomas

Prolactinomas represent the most common type of functioning pituitary tumors in children and adolescents, with a marked female predominance and often with a genetic predisposition (eg, *MEN1* and *AIP* pathogenic variants). The diagnosis is based on hyperprolactinemia and imaging. Dopamine agonists are the first-line therapy and are effective and safe for tumor volume reduction, while surgery can be considered in cases of dopamine agonist intolerance or resistance, in emergency situations such as threatened visual function and apoplexy, or in young patients with a well-delineated microadenoma and a high likelihood of surgical cure. The possibility of delaying surgery until age 18 years (to obtain adult consent) should be considered in cases of microadenomas. Radiotherapy is effective in controlling tumor growth but is less effective in normalizing prolactin levels. Hence, radiotherapy should be reserved for aggressive and refractory prolactinomas.³⁶

Cushing Disease

In pediatric Cushing disease, central weight gain, facial changes, and growth failure are almost the rule, whereas hypertension, fatigability, purple striae, skin fragility, virilization, sleep disorders, diabetes, and stress fractures are less common.³⁷

Similar treatment algorithms with adults may be followed. Corticotroph adenomas are often small and less often visualized on MRI. Few pituitary surgeons are experienced in operating on children, and surgery may be technically more difficult in very young children.³⁸ Successful surgery for pediatric Cushing disease may result in hypopituitarism, and long-term endocrine follow-up and GH testing are mandatory. In cases of surgical failure or disease recurrence, repeat surgery may be considered, provided the tumor is visible and seemingly resectable. For children with Cushing disease who do not achieve remission, medical therapy is required. Radiotherapy may also be considered in such patients, and all patients who have undergone radiotherapy should be monitored for the development of GHD. Ketoconazole, metyrapone, and, more recently, osilodrostat have been used with some success, but no large trials have been published.³⁹ Other pituitary-directed cortisol-lowering treatments, such as cabergoline or pasireotide, have not yet been validated in children. Bilateral adrenalectomy is a radical but salvage therapeutic option only to be considered in life-threatening situations when other therapeutic options have failed or are not indicated.

Somatotropinomas

GH excess is rare in pediatric patients, and a GH-secreting pituitary adenoma is the main cause of acromegaly/acrogigantism, but diffuse pituitary hyperplasia or multiple adenomas may also be observed in individuals with McCune-Albright syndrome, Carney complex, X-linked acrogigantism, or GHRH-secreting tumors. Childhood-onset GH-secreting adenoma or hyperplasia is the most likely condition to have an identifiable genetic cause, the most frequent of which are *AIP* germline pathogenic variants and duplications in the *GPR101* gene, the latter being responsible for X-linked acrogigantism. Most somatotropinomas are macroadenomas at diagnosis, and are frequently invasive and difficult to control, with a high recurrence risk.⁴⁰ Similar to treatment options for adults, pediatric patients' options include surgery, medical

therapy, and radiotherapy. However, complete remission rates tend to be lower in children than in adults. Hypopituitarism is a frequent surgical complication in acrogigantism.⁴¹ Regarding medical therapy, first-generation somatostatin analogues (octreotide and lanreotide) are considered, and pegvisomant is more effective in patients with genetic forms of GH excess, especially those with *AIP* and *GPR101* pathogenic variants,⁴⁰ whereas experience with pasireotide is still lacking. Dopamine agonists, primarily cabergoline, may be used alone or combined with somatostatin analogues, but their efficacy is modest in children.

Conclusion

Transition age represents a challenging time because patients usually transition from childhood, which is associated with parental dependence, to a new sense of independence, and thus adherence to medical treatment and regular follow-up may be more problematic. Treatment options must be tailored to the patient and based on the underlying condition and specific patient characteristics. A multidisciplinary approach is crucial in the optimal management of adolescent pituitary tumor survivors. These young people are undergoing major life changes, and their medical care must take them into account. Special transition clinics involving both pediatric and adult endocrinologists can improve care, promote continuity, reassess the hypothalamic-pituitary axis, and enhance treatment adherence. Close rapport and understanding between pediatricians and adult endocrinologists regarding the patient's lifestyle changes and concerns will facilitate successful transition from pediatric to adult endocrine care services.

Clinical Case Vignettes

Case 1

An 18-year-old woman was diagnosed with a craniopharyngioma at age 14 years, and she underwent surgical resection, with resultant panhypopituitarism. She has been on a replacement regimen with levothyroxine, hydrocortisone, and GH. An oral contraceptive was recently commenced for estrogen and progesterone replacement. Over the past 12 months, she has only grown 1 cm, and her height now is 62 in (157.5 cm). A recent X-ray of her hand and wrist shows almost complete epiphyseal closure. She ran out of GH and has been off therapy for 3 months. Her most recent IGF-1 SDS is -2.4. She inquires if she still needs to continue GH treatment, as she is “tired” of the daily GH injections.

If she does not continue GH treatment, which of the following is she most at risk of developing?

- A. Weight gain
- B. Decreased fasting glucose
- C. Impaired quality of life
- D. Increased BMI
- E. Decreased peak bone mass

Answer: E) Decreased peak bone mass

The *transition period* refers to the time of life when puberty ends and full maturation of muscle, bone, and body fat composition takes place. Peak bone mass typically occurs around age 22.3 years for females and later for males, around age 26.9 years.⁴² Untreated GHD during the transition period results in failure to attain this peak bone mass (Answer E). When GH is discontinued, body composition changes are likely to take place (decreased lean mass and increased fat mass), but overall weight does not increase noticeably (Answer A), especially in young adults. Discontinuation of GH treatment after final adult height is achieved during the transition period induces unfavorable changes in body

composition (increased fat mass and decreased lean body mass) (Answer D), which does not necessarily compromise insulin sensitivity and glucose metabolism (Answer B).⁴³ Importantly, the unfavorable changes in body composition can be reversed with resumption of GH treatment.⁴⁴ Additionally, quality of life has been shown to be affected in adults with untreated GHD⁴⁴; however, several studies have found no impairments of quality of life (Answer C) in the transition period of patients with GHD who continued GH treatment,⁴⁶ or shortly after the discontinuation of GH treatment during the transition period.⁴⁷

Case 2

A 19-year-old man is seen in the clinic for evaluation of headaches, decreased libido, and worsening fatigue. MRI reveals a 12-mm Rathke cleft cyst. On further questioning, he recalls a period 2 years ago when he experienced increased thirst and urinary frequency that has since resolved. On physical examination, he has a sallow complexion, minimal facial hair, and a normal-sized phallus and testes.

Laboratory test results (sample drawn at 9 AM):

Sodium = 145 mEq/L (135-145 mEq/L)
(SI: 145 mmol/L [135-145 mmol/L])
Potassium = 3.8 mEq/L (5.5-5.0 mEq/L)
(SI: 3.8 mmol/L [3.5-5.0 mmol/L])
Urine specific gravity = 1.004
Serum cortisol = 6.4 µg/dL (6.0-18.4 µg/dL)
(SI: 176.6 nmol/L [165.5-507.6 nmol/L])
ACTH = 15 pg/mL (6-50 pg/mL) (SI: 3.3 pmol/L [1.3-11.0 pmol/L])
Free T₄ = 0.7 ng/mL (0.8-1.8 ng/mL)
(SI: 9.00 pmol/L [10.30-23.17 pmol/L])
TSH = 1.6 mIU/L (0.5-5.0 mIU/L)
Testosterone = 274 ng/dL (300-900 ng/dL)
(SI: 9.5 nmol/L [10.4-31.2 nmol/L])

Which of the following should you counsel the patient to be aware of upon the initiation of hydrocortisone and levothyroxine?

- A. Hyponatremia
- B. Orthostatic hypotension
- C. Decrease in libido
- D. Heart palpitations
- E. Increased thirst and urination

Answer: E) Increased thirst and urination

Chronic deficiencies of cortisol and thyroid hormones increase the sensitivity of AVP receptors in the kidneys to AVP. Thus, upon replacement of these hormones, the small amount of AVP secreted in patients with partial AVP deficiency may no longer be sufficient to impact water reabsorption in the kidneys, resulting in subclinical AVP deficiency that may manifest as increased thirst and urination (Answer E). AVP deficiency can present immediately after GC initiation or within several weeks. The mechanisms of adrenal insufficiency that impair renal water excretion are both AVP-dependent and AVP-independent. First, cortisol induces relative resistance of the V2 receptor to AVP. Thus, in cases of adrenal insufficiency, AVP's effects are amplified. Second, corticotropin-releasing hormone neurons in the paraventricular nucleus stimulate the release of ACTH and AVP. Additionally, corticotropin-releasing hormone is upregulated in states of adrenal insufficiency, thereby stimulating AVP release. Third, adrenal insufficiency results in renal sodium loss and volume depletion, potent stimuli for AVP release. Lastly, adrenal insufficiency leads to decreased stroke volume and cardiac output, resulting in nonosmotic stimulation of AVP secretion. Therefore, care should be taken when secondary adrenal insufficiency is encountered, as AVP deficiency may manifest after GC administration. Hyponatremia, not hyponatremia (Answer A), may occur with untreated AVP deficiency. Initiation of physiologic doses of hydrocortisone should not cause orthostatic hypotension (Answer B) or decrease libido (Answer C), and physiologic doses of levothyroxine should not cause heart palpitations

(Answer D) in a young patient. However, administration of levothyroxine alone, even at physiologic doses, can unmask adrenal insufficiency.

Case 3

A 20-year-old man who underwent surgical removal of a nonfunctioning pituitary macroadenoma 3 years ago has developed hypopituitarism. He currently takes levothyroxine, hydrocortisone, and injectable testosterone cypionate. He transitioned to adult services 1 year ago. He has attended today's clinic visit alone and is fully independent. He has started to question his treatments because he finds it difficult to take his medications regularly. He has a normal libido and erectile function and is considering fertility in the near future. On physical examination, he is well virilized with 18 cc testes bilaterally with normal consistency.

Which of the following is the best next step in this patient's management?

- A. Obtain semen analysis
- B. Switch from testosterone to clomiphene citrate
- C. Switch from testosterone to hCG injections
- D. Switch from testosterone to hCG and FSH injections
- E. Increase the testosterone dosage

Answer: A) Obtain semen analysis

The best next step is to establish whether this patient is truly infertile by obtaining a semen analysis (Answer A). Although one would expect that he might be (given his hypopituitarism and being on testosterone replacement therapy), he might have adequate sperm counts and morphology for fertility. Drincic et al⁴⁸ found that adequate spermatogenesis for fertility is reported in about 50% of men with acquired hypogonadotropic hypogonadism. Fertility discussions in transition clinics are important conversations that need to be undertaken before starting testosterone replacement therapy, especially for patients older than 17 years, to address impacts on future family-building. If

this patient is found to have azoospermia or oligospermia on semen analysis, he might respond to hCG injections (Answer C) and might also need FSH injections (Answer D). Trying hCG and FSH therapies without assessing his fertility status is not appropriate. Clomiphene citrate (Answer B), an estrogen receptor antagonist, would not be expected to effectively stimulate gonadotropin production in a patient with hypopituitarism. Increasing the testosterone dosage (Answer E) would not improve his fertility; rather, it could further impair fertility by suppressing gonadotropins, thus reducing spermatogenesis.

Key Learning Points

- Transitioning pituitary tumor survivors is a challenging and individualized process, necessitating an individualized and multidisciplinary approach.
- The transition period is a critical and vulnerable time for pituitary tumor survivors, requiring specialized attention to evolving endocrine changes and needs.
- Ongoing reassessment of hormonal status is essential during transition, as pituitary function can change. This requires periodic endocrine testing, particularly for conditions like GHD, where retesting after cessation of linear growth is recommended to avoid unnecessary lifelong therapy or, conversely, to ensure continued necessary GH replacement.
- Effective transition requires a coordinated, multidisciplinary effort with structured communication between pediatric and adult endocrinologists, and patient engagement through adequate preparation and education on self-management.
- Continued management of pituitary hormone deficiencies during transition presents unique challenges that require individualized management, while acknowledging the physiological changes that occur during this period.

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REPRODUCTIVE ENDOCRINOLOGY

Endocrine and Fertility Implications After Anabolic Steroids, Hormonal Contraception, and Gender-Affirming Hormone Therapy

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe how exogenous sex steroids suppress the hypothalamic-pituitary-gonadal (HPG) axis.
 - Identify clinical patterns of endocrine and fertility recovery following the cessation of exogenous hormones.
 - Recognize diagnostic and therapeutic approaches to support recovery of gonadal function and counsel patients in these trajectories.
-

Significance of the Clinical Problem

Pharmacologic manipulation of the HPG axis occurs in several medical and nonmedical contexts. Clinicians increasingly encounter individuals who previously used exogenous sex steroids and subsequently seek evaluation of endocrine function or fertility. Common scenarios include prior use of anabolic-androgenic steroids (AAS) in athletes or bodybuilders, discontinuation of

hormonal contraception in individuals attempting to conceive, and patients who have used gender-affirming hormone therapy (GAHT) and wish to explore fertility options.

All these exposures share a common biological mechanism: suppression of endogenous gonadal function through negative feedback on the HPG axis. While this suppression is usually reversible, recovery of hormonal function and fertility is highly variable and depends on several factors, including the duration of hormone exposure, cumulative dose, age, and underlying reproductive health.

For many patients, cessation of exogenous hormones leads to gradual restoration of the HPG axis and recovery of reproductive function. However, the time course of recovery ranges from weeks to several years, and in some individuals recovery may be incomplete. These uncertainties can generate significant clinical challenges, particularly in the context of infertility counseling.

The increasing prevalence of AAS use, broader access to GAHT, and widespread use of hormonal contraception have all contributed to a growing number of patients seeking guidance regarding recovery of gonadal function. As a result, clinicians in endocrinology and reproductive medicine must be familiar with the mechanisms of HPG suppression, expected recovery trajectories, and

potential interventions to facilitate the restoration of endocrine and reproductive function.

Practice Gaps

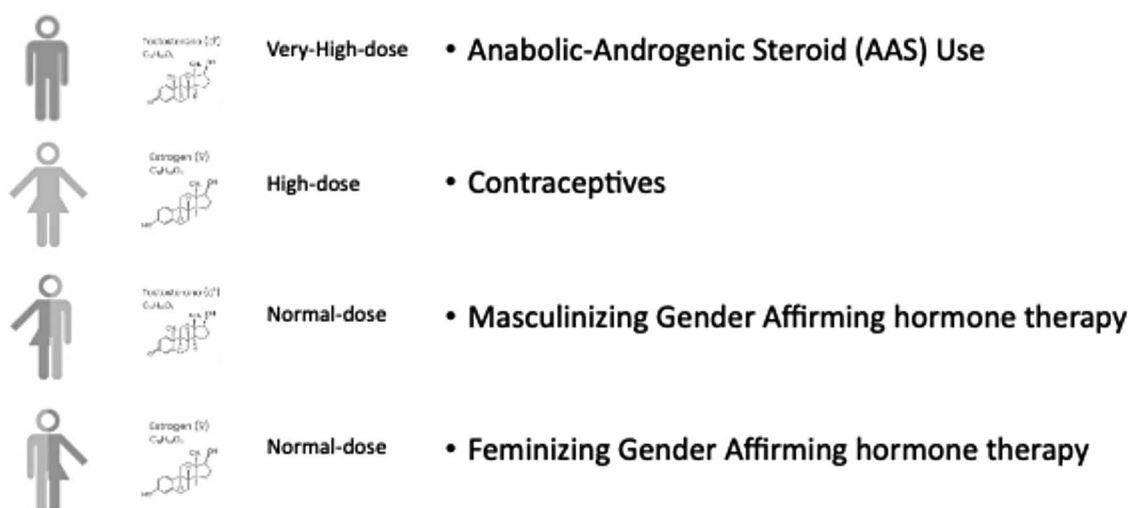
- Many clinicians are unaware of the variability in recovery of the HPG axis after exogenous hormone exposure. Although suppression is often reversible, the duration of recovery can be prolonged and unpredictable, particularly after supraphysiologic androgen exposure.
- Counseling regarding fertility implications is inconsistently provided before starting hormone therapy. This is especially relevant for individuals initiating GAHT or using anabolic steroids without medical supervision.
- Therapeutic strategies to support recovery of gonadal function are underused. Pharmacologic approaches to stimulate endogenous gonadotropin secretion and restore spermatogenesis are available. Also, clomiphene can be used, although this is less well documented.

Discussion

Different Contexts of Sex Hormone Use

The use of exogenous hormones occurs across a wide range of medical and social contexts. Prominent examples include AAS use, hormonal contraception, and GAHT (*Figure*). Although these forms of hormone use differ substantially in their purpose, patterns of access, social acceptance, and degree of medical supervision, they share a common physiological effect: suppression of the HPG axis. Through negative feedback mechanisms, exogenous sex steroids reduce endogenous gonadotropin secretion, resulting in decreased gonadal hormone production and impaired reproductive function in both males and females. Considering these different forms of gonadal suppression together may provide a more comprehensive perspective on the mechanisms, duration, and variability of endocrine recovery following cessation of exogenous hormone exposure. Such an integrative approach may improve understanding of HPG-axis dynamics, inform clinical management of recovery, and help contextualize the endocrine consequences of hormone use across both medical and nonmedical settings.

Figure. Sex Hormone Use in Different Contexts



Physiology of the HPG Axis

The HPG axis regulates reproductive endocrine function through a tightly coordinated hormonal signaling system.^{1,2} Sex steroids produced by the gonads exert negative feedback at both the hypothalamic and pituitary levels. Specifically, estradiol reduces GnRH pulsatility and suppresses LH and FSH secretion. A substantial proportion of the negative feedback exerted by testosterone on the HPG axis is mediated through its aromatization to estradiol.³ The locally produced estradiol then binds primarily to estrogen receptor- α (ER α), which is abundantly expressed in hypothalamic nuclei involved in reproductive control. Activation of these receptors suppresses the pulsatile secretion of GnRH from hypothalamic neurons. Evidence for this mechanism comes from clinical and experimental studies showing that inhibition of aromatase increases LH and testosterone concentrations, while administration of estradiol strongly suppresses gonadotropin secretion in men.¹

Exogenous sex steroids exploit this physiologic feedback system. When circulating levels of androgens or estrogens rise due to external administration, endogenous gonadotropin secretion is suppressed. As a result, gonadal steroidogenesis and gametogenesis decline. The degree of suppression depends on the type, dose, and duration of hormone exposure. In many cases, suppression is reversible, but prolonged exposure can lead to extended recovery periods.

Recovery of Gonadal Function After AAS Use

AASs are synthetic derivatives of testosterone used medically for specific conditions but widely used outside medical supervision to enhance muscle mass and athletic performance. Supraphysiologic doses of these agents strongly suppress LH and FSH secretion through negative feedback at the hypothalamus and pituitary. The resulting endocrine state resembles hypogonadotropic hypogonadism. Serum testosterone may remain low after cessation of steroid use due to persistent

suppression of the HPG axis. At the testicular level, reduced intratesticular testosterone leads to impaired spermatogenesis and testicular atrophy.

The recovery process following discontinuation of anabolic steroids involves gradual restoration of hypothalamic GnRH pulsatility, followed by recovery of pituitary gonadotropin secretion. Once LH and FSH levels normalize, endogenous testosterone production and spermatogenesis may gradually resume. Recovery of gonadal function after AAS discontinuation follows a gradual pattern, with gonadotropin levels (LH and FSH) returning to baseline within 13 to 24 weeks,⁴ testosterone normalizing within 3 months in most users,⁵ and spermatogenesis requiring approximately 1 year for recovery.⁶ Factors associated with prolonged recovery include longer duration of steroid exposure, higher cumulative doses, use of multiple androgenic compounds, and increasing age. However, recovery remains incomplete in a substantial proportion of users,⁷ with 11% to 34% showing persistent abnormalities at 1-year follow-up, and only 4 of 38 patients with known outcomes achieving complete reversibility in 1 systematic review.⁴ Recovery of spermatogenesis typically occurs later than recovery of testosterone production because spermatogenesis requires several months to complete a full cycle.

Diagnostic monitoring employs hormone assays (LH, FSH, testosterone, inhibin B), semen analysis parameters, and physical examination, including testicular volume measurement. Management strategies may include pharmacologic stimulation of the HPG axis. Selective estrogen receptor modulators, such as clomiphene citrate, increase endogenous gonadotropin secretion by blocking estrogen-mediated negative feedback at the hypothalamus. hCG can stimulate Leydig cells to produce testosterone, while FSH therapy may be required to directly stimulate spermatogenesis in severe cases.⁸

Recovery outcomes are strongly influenced by AAS exposure characteristics, with negative correlations between recovery and duration of use, dose, and number of concurrent agents. Younger

age and oligospermia rather than azoospermia at baseline predict better outcomes, while high cumulative lifetime doses and prolonged use increase the risk of permanent dysfunction.⁹

Recovery After Hormonal Contraception

Hormonal contraceptives represent one of the most common forms of pharmacologic suppression of the HPG axis. Combined oral contraceptives contain estrogen and progestin, which inhibit ovulation by suppressing gonadotropin secretion. During active use of combined hormonal contraception, ovulation does not occur and endogenous ovarian steroid production is suppressed. After cessation of oral contraceptives, the exogenous hormonal feedback is removed, allowing the HPG axis to gradually resume its normal activity. GnRH pulsatility typically recovers first, followed by normalization of FSH and LH secretion. Increased FSH levels stimulate follicular recruitment and growth in the ovaries, while the midcycle LH surge is required to trigger ovulation. In many women, ovulatory cycles resume relatively quickly.¹⁰⁻¹³ Studies have shown that most women experience the return of ovulation within 1 to 3 months after stopping combined oral contraceptives. However, the timing of recovery can vary depending on individual factors such as age, duration of contraceptive use, underlying menstrual irregularities, and body composition. Epidemiological studies consistently demonstrate that cumulative pregnancy rates within 1 year after discontinuation of oral contraceptives are comparable to those observed in women who previously used nonhormonal contraceptive methods.¹⁰⁻¹³

Recovery After GAHT

GAHT is used by transgender individuals to align physical characteristics with gender identity. These therapies involve exogenous sex steroids that intentionally suppress endogenous gonadal hormone production.

Transgender Women

Transgender women (individuals assigned male at birth who identify as female) typically receive estradiol therapy combined with agents that suppress testosterone production. Antiandrogens such as spironolactone or cyproterone acetate are commonly used, and some individuals receive GnRH analogues. These therapies reduce circulating testosterone levels and suppress spermatogenesis. Histologic examination of testicular tissue in individuals receiving estrogen therapy has demonstrated decreased seminiferous tubule diameter and impaired germ-cell maturation.

While suppression of spermatogenesis is common during therapy, recovery after discontinuation appears possible in some individuals. Case reports and small observational studies suggest that sperm production may return several months after cessation of hormone therapy, although the time course is variable. One study found recovery of viable spermatozoa in 9 transwomen who stopped estrogen therapy, suggesting reversibility is possible.¹⁴ However, a systematic review notes that while recovery after cessation may occur, questions about reversibility remain, particularly for those starting transition young.¹⁵ Because recovery is unpredictable, fertility preservation before initiation of GAHT is recommended whenever possible.

Transgender Men

Transgender men (individuals assigned female at birth who identify as male) typically receive testosterone therapy to induce masculinizing physical changes. Testosterone suppresses ovulation and usually leads to amenorrhea within several months. Despite suppression of ovarian function, ovarian follicles often remain present during testosterone therapy. After discontinuation of testosterone, ovulation may resume in many individuals. Pregnancies have been reported after cessation of testosterone therapy, even in individuals who used testosterone for several years. However, the time required for ovulatory recovery can vary.

One study followed 56 transgender men prospectively and found antimüllerian hormone levels remained within normal ranges despite slight decreases; notably, 4 men fathered biological children after up to 12 years of testosterone treatment.¹⁶ So, current evidence suggests that ovarian reserve may remain preserved in many individuals receiving testosterone therapy, although long-term data are limited.¹⁷⁻¹⁸

Clinical Case Vignettes

Case 1

A 34-year-old man presents with fatigue, low libido, and infertility. He used AAS intermittently for bodybuilding over a 5-year period and discontinued them 10 months ago.

Laboratory test results:

Total testosterone, low
LH, suppressed
FSH, suppressed
Semen analysis, azoospermia

Which of the following is the most appropriate next step in management?

- A. Begin testosterone replacement therapy
- B. Begin clomiphene citrate
- C. Perform testicular biopsy
- D. Begin aromatase inhibitor therapy
- E. Recommend observation only

Answer: B) Begin clomiphene citrate

Testosterone replacement therapy would further suppress gonadotropin secretion and worsen infertility. Clomiphene citrate increases endogenous gonadotropin secretion by blocking estrogen feedback at the hypothalamus.

Case 2

A 38-year-old man presents with infertility 2 years after stopping AAS use for competitive bodybuilding. He reports no other medical problems.

Laboratory test results:

Testosterone, low
LH, suppressed
FSH, suppressed
Semen, azoospermia

Which of the following therapies is most likely to stimulate spermatogenesis?

- A. Testosterone injections
- B. hCG monotherapy
- C. hCG combined with FSH therapy
- D. GnRH antagonist therapy
- E. Aromatase inhibitor monotherapy

Answer: C) hCG combined with FSH therapy

Combined therapy stimulates both Leydig-cell testosterone production and Sertoli-cell function, thereby promoting spermatogenesis. hCG monotherapy might be tried as an initial step.

Case 3

A 25-year-old transgender woman has been receiving estradiol therapy with an antiandrogen (GnRH agonist) for 4 years. She now wishes to explore fertility options.

Which counseling statement is most accurate?

- A. Fertility is permanently lost after 2 years of estrogen therapy
- B. Spermatogenesis may recover after discontinuation of hormone therapy
- C. Sperm production returns immediately after stopping hormone therapy
- D. Estrogen therapy permanently destroys germ cells
- E. Fertility preservation is not possible

Answer: B) Spermatogenesis may recover after discontinuation of hormone therapy

Spermatogenesis may recover in this setting, but it is unpredictable.

Key Learning Points

- Exogenous sex steroids suppress the HPG axis through negative feedback mechanisms.
- For testosterone, feedback occurs mainly through aromatization to estradiol.
- Recovery of gonadal endocrine function and fertility after hormone exposure is variable and influenced by duration of exposure, dosage, and baseline gonadal reserve.
- AAS use can lead to prolonged hypogonadotropic hypogonadism and infertility.
- Fertility typically returns rapidly after discontinuation of hormonal contraception.
- Recovery of reproductive function after GAHT is possible but unpredictable.
- Fertility preservation counseling should be provided before initiation of therapies that suppress gonadal function.

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Update on the Management of Androgen Insensitivity Syndromes

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify symptoms and initiate appropriate investigations to diagnose androgen insensitivity syndrome (AIS) in men and women.
- Manage hormone treatment for adolescents and adults with complete AIS (CAIS) and partial AIS (PAIS), including long-term consequences.
- Manage malignancy risk, ongoing assessment, and follow-up for AIS.

Significance of the Clinical Problem

Complete Androgen Insensitivity Syndrome

CAIS is characterized by a complete absence of androgen receptor (AR) function.¹ Affected girls have female external genitalia, and the Wolffian structures (male internal genitalia) do not differentiate fully despite testosterone produced by Leydig cells in the testes. Antimüllerian hormone (AMH), produced by the Sertoli cells, results in the absence of the uterus, fallopian tubes, and the upper part of the vagina. In almost half of cases, CAIS is diagnosed in early childhood

when the girl is evaluated for an inguinal hernia. Most girls are diagnosed during or after puberty with primary amenorrhea. Girls with retained gonads have normal breast development due to aromatization of testosterone and may have tall stature and little or no pubic and axillary hair.^{2,3} Gender identity is almost exclusively female. Laboratory testing shows testosterone in the male range, FSH within the normal range, and often elevated LH, resulting in an elevated LH-to-FSH ratio due to estrogen-mediated central feedback.⁴ Karyotype is 46,XY, and there is no detectable uterus on ultrasonography. In more than 95% of the cases, a loss-of-function variant is detected in the AR gene. Girls with retained gonads often undergo spontaneous puberty with breast development. Malignancy risk is considered low before adolescence. They may, however, virilize during puberty if the AR activity is not completely abolished. In individuals raised as girls and who have gonads removed early in life, hormone treatment with estradiol is mandatory for puberty induction. Puberty treatment should start at an appropriate age, similar to when their peers start puberty, at 10 or 11 years of age,⁵ and continue into adulthood.

Partial Androgen Insensitivity Syndrome

PAIS presents with a wide range of clinical signs at birth, from mild virilization in a girl to severe hypospadias and undescended testes in

a boy. PAIS is often diagnosed in the neonatal period after referral to a multidisciplinary team due to suspicion of a difference of sex development (DSD). Discussions may include decisions about the sex of rearing. Diagnostic workup, psychological support, and a follow-up and treatment plan then follow.⁶ The degree of virilization at birth can be graded using the external masculinization score (EMS) or external genitalia score (EGS).⁷ In PAIS, a pathogenic variant in the *AR* gene is identified in less than 30% of cases.⁸ A girl with severe PAIS may be diagnosed during evaluation for increased virilization in puberty. This may cause considerable distress, and in some cases, a change in gender. Previously undiagnosed boys with a history of surgery for hypospadias may come to medical attention during puberty due to marked gynecomastia or unsatisfactory pubertal progression.⁵ The masculinization score at birth is a good predictor of pubertal development and possible need for testosterone treatment, and has been shown to be a better predictor for pubertal development than the genetic variant/genetic assessment.⁹ The degree of AIS is reflected in the clinical signs at puberty. Affected boys often develop less body hair and facial hair (beard) and have a smaller penis and smaller testicular volumes. Psychological evaluation and assessment of gender contentedness and gender issues should be performed by a multidisciplinary team and by an experienced psychologist before starting hormone treatment.⁵ Laboratory tests show FSH within the normal range and often higher LH, resulting in an elevated LH-to-FSH ratio.⁴ LH is more elevated, and the difference is more pronounced in adolescents and adults than in newborns, yielding a higher ratio. Inhibin B and AMH are within the normal range before puberty, but after puberty, AMH is relatively high and inhibin B is usually within the normal range.¹⁰ In some cases, when a variant in the *AR* gene is not identified, pathogenic variants have been found in noncoding and intronic regions, or within *AR* coregulators. There may also be an oligogenic cause with a combination of affected

genes resulting in PAIS.⁸ The PAIS phenotype is variable, even among individuals with the same *AR* pathogenic variant within the same family.^{8,10,11}

Sexual Health, Well-Being, and Quality of Life in CAIS and PAIS

Sexual health and fertility are affected in both CAIS and PAIS. Sexual and social well-being are important aspects of life and should be considered in treatment. Body satisfaction and self-esteem need to be addressed, as they affect quality of life. Impaired sexual function has been reported in CAIS, possibly related to a relatively shorter vagina, less lubrication, and psychological factors.¹² However, others have reported a satisfactory sexual life.^{13,14} In CAIS, pregnancy cannot occur, and no fertility treatments are currently available for this patient population.

Most follow-up studies in men have focused on those with hypospadias, regardless of genetic background, and only a few have focused specifically on men with AIS. A systematic review of adult sexual function after hypospadias surgery, including 13 studies,¹⁵ was recently published. The authors report erectile dysfunction in 12% and sexual dissatisfaction in 16%. The situation may be more difficult for men with PAIS, as a French study reported erectile dysfunction in almost 50%.¹⁶ Seventeen men with PAIS were included in the European dsdLIFE study. Their penile length was 46 mm ± 21 mm, the scrotum was often bifid or hypoplastic, 14 patients were dissatisfied with penis size, and only half were satisfied with erectile function.¹⁷ There are only a few published cases of men with PAIS who have been able to father a child, either spontaneously or after special treatment.

Practice Gaps

- Hormonal treatment of individuals with CAIS and PAIS in puberty and adult life needs to be individualized. We are just beginning to understand the long-term issues that develop with age and how to manage them.

- How large is the risk of gonadal malignancy with increasing age and over time? The discussion regarding the need for gonadectomy and how retained gonads should be followed up is ongoing and controversial.
- Sexual health is affected in CAIS and PAIS in both men and women, resulting in negative effects on general well-being. Can optimizing hormonal and psychological treatment and care improve psychosocial well-being and quality of life?

Discussion

Malignancy Risk

The increased risk of gonadal malignancy in individuals with AIS influences clinical decisions and follow-up. Because of this risk, gonadectomy was historically performed at diagnosis in virtually all individuals brought up as girls, even when diagnosed before puberty. Today, the timing of gonadectomy is debated because the lifetime risk of invasive tumor development is uncertain. Gonadectomy is often delayed to allow for the possibility of spontaneous puberty, which most consider beneficial. Gonadal biopsies to assess the risk of malignancy are then performed in late puberty. In adolescence, the patient can be involved in the decision regarding gonadectomy. The risk assessment is supported by evidence that gonadal germ-cell cancer and germ-cell neoplasia in situ are associated with the presence of testis-specific protein on Y (TSPY) on the Y chromosome.¹⁸ There are histological and immunohistochemical criteria for germ-cell neoplasia in situ, including OCT3/4 expression or coexpression of TSPY and KITLG. The lifetime risk of germ-cell cancer is unknown, but the risk is low before puberty. Full and thorough disclosure, along with repeated information, from all team members, is essential to this shared decision-making process.¹⁹ However, current practice varies across countries and centers, with gonadectomy recommended in early adulthood for CAIS in 67% of centers, and 35% of men with PAIS have retained gonads.

The positive effects of retaining the gonads after puberty must be weighed against the malignancy risk and the required follow-up, as appreciated or experienced by the individual. This, of course, differs for each patient and between women and men.

When the gonads are retained after puberty, patient education and careful follow-up are necessary. Various algorithms for the management and follow-up of the gonads have been suggested. Regular analyses of tumor markers, including α -fetoprotein, hCG, and lactate dehydrogenase, have been suggested. The drawback of these markers is that their levels rise as the tumor progresses beyond the in situ stage. Frequent or yearly ultrasonography or MR scans have been suggested. Gonadopexy to facilitate visualization of intra-abdominal gonads has been performed.²⁰ Repeated gonadal biopsies after 10 years have also been suggested. When the gonads are palpable, regular self-examination is recommended.²¹⁻²³

Hormone Treatment

After gonadectomy, hormone replacement is necessary in both men and women. Women with retained gonads may have satisfactory estrogen levels; however, supplemental estrogen may be required. In general, transdermal estrogen is recommended because it avoids first-pass liver effects.²⁴ Estrogen positively affects bone health. Women with CAIS should not be treated with progesterone or progestin because they do not have a uterus. Despite reported good adherence to hormone therapy, hormone levels may vary considerably. The reason for this is insufficiently studied, underscoring the importance of follow-up with blood samples.²⁵

There are no generally accepted guidelines for hormone replacement in CAIS, but the recently published guidelines for hormone replacement therapy/menopause can serve as a reference.²⁶ Premenopausal treatment with 100 to 200 mcg transdermal (equivalent to 2 to 4 mg micronized 17 β -estradiol) should be followed by blood sampling.

Testosterone treatment in women with CAIS has been discussed based on the argument that it would be more physiological and that patient groups have reported feeling better on testosterone than on estrogen.²⁷ A German multicenter crossover trial of 26 patients with CAIS assessed the short-term effects of transdermal estrogen vs testosterone.²⁸ Estradiol, 1.5 mg daily, was given for 6 months, followed by crossover to testosterone, 50 mg daily for 6 months. Testosterone treatment showed a positive effect on the female sexual function index (FSFI) for sexual desire but had no other significant effects. No virilization was observed, and gonadotropin concentrations remained stable in both treatment groups. A possible worsening of metabolic parameters, such as BMI and lipid profile, was observed, but this was not significant.²⁸

In men who have had gonadectomy, testosterone treatment needs to be individualized, and higher dosages are often required. Due to the degree of androgen insensitivity, the response is highly variable. The aim is to normalize body hair and penis size as much as possible. Follow-up with assessment of LH, hematocrit, and possibly liver enzymes for safety may be considered.¹¹

Sexual Health

Women With CAIS or PAIS

In a cross-sectional study of 66 women with CAIS, 24 were recruited from a clinic and 42 from a support group. The study showed that 90% had some difficulties with sexual function and vaginal penetration. Although 77% of the study participants had the perception that they had a small vagina, vaginal hypoplasia was only found in 35% on examination. The authors concluded that both vaginal hypoplasia and psychological issues contributed to sexual difficulties.¹² Other studies have reported less negative results and overall satisfying sexual function in 20 and 22 women, respectively.^{13,14}

Vaginoplasty was historically the most common procedure, followed by self-dilatation. In recent years, vaginal dilatations have become

the first-line treatment and have often proven successful. The elastic tissue of the sinovaginal bulb, the lower part of the vagina, enables this.^{29,30}

An Italian study of 34 women with CAIS used questionnaires for assessing sexual function (FSFI), sexual distress (FSDS-R), and body uneasiness to relate results to treatment and hormone levels. Despite hormone therapy and reported optimal compliance, 69% had estradiol levels less than 50 pg/mL (<180 pmol/L). The study showed that, even with reported good adherence to hormone therapy, hormone levels vary considerably. Outcomes were better among those with higher estrogen levels at follow-up. This underscores the importance of monitoring treatment with blood samples and adjusting treatment accordingly.

Boys and Men With PAIS

Men with PAIS report impaired sexual health and function due to small penis size and erectile dysfunction, although this has been insufficiently studied. Interventions to improve outcomes for these boys as they grow up have been tried, but their effects vary substantially, and no controlled studies have been conducted. In a newborn with undermasculinization and a diagnosis of PAIS, the DSD team and the parents make the decision on the sex of rearing. If the child is raised as a boy, topical treatment with testosterone or dihydrotestosterone can be tried. Preferably, this should be done during the first year, or first 6 months, of life, during mini-puberty. Treatment during puberty can also be considered. The underlying pathogenesis of pubertal development is the low affinity of testosterone for the AR. Adding testosterone can be considered in mid-puberty after assessment of puberty, both clinically and with laboratory testing. If there are signs of hypoandrogenism, extra transdermal testosterone can be tried³¹ by administering supraphysiological doses of testosterone.⁵ The aim is to increase facial and pubic hair, as well as penis size. However, there are no controlled trials, and responses are highly variable. Follow-up with assessment of LH, hematocrit, and possibly liver enzymes for safety has been suggested.¹¹

Gynecomastia can be a problem for boys and men with PAIS. It is thought to be related to an imbalance between testosterone and estrogen effects, but it may also be influenced by hormone levels. Aromatase inhibitors may improve gynecomastia when started early.^{10,11,32} Gynecomastia is more common in boys/men with PAIS and a small penis, possibly reflecting the degree of androgen sensitivity. Testosterone treatment may lower LH, which in turn may reduce LH-induced aromatase activity, but it may also worsen the situation if estrogen levels increase. Estrogen receptor blockade may be tried.^{33,34} An alternative approach is to treat with dihydrotestosterone, which does not aromatize. However, there are no randomized controlled trials demonstrating the effectiveness of this treatment. In many cases, surgery is required.

Multidisciplinary Team Care and Psychological Support

The psychological and psychosocial impact of AIS is often considerable and important to address. In the dsdLIFE follow-up of 1040 individuals, 50% reported a need for psychological care.³⁵ Sexual health and fertility issues need to be addressed, as do gender issues and gender contentment, which is especially important when starting hormone replacement. Gender change is extremely rare in women with CAIS. Among individuals with PAIS, gender change has historically been described in up to 25%, both from male to female and from female to male, but more recent studies are lacking.

Challenging issues related to replacement therapies, bone health, psychological well-being, and cardiometabolic health must be considered in the long term (*Box*). Multidisciplinary team care in highly specialized clinics involving several disciplines, including endocrinology, surgery, psychology, sexology, gynecology, and andrology, is therefore essential.^{36,37}

Box. Clinical and Laboratory Follow Up

Clinical

- Weight, height
- Clinical status
- Blood pressure

Laboratory

- FSH, LH
- Testosterone
- Estradiol
- Blood cell count
- Fasting blood glucose, hemoglobin A_{1c}
- Kidney and liver function
- Lipid status
- Vitamin D, calcium, DXA

Clinical Case Vignettes

Case 1

An 18-year-old woman seeks medical attention because she has only had one menstrual bleed several years ago, but none thereafter. She is now starting college and is active in competitive sports. Her height is 67 in (170 cm), and weight is 141 lb (64 kg) (BMI = 22 kg/m²). She has breast development. Somatic status, including pubertal development, shows B4, sparse pubic hair, and no acne. Her blood pressure is 100/57 mm Hg.

Which of the following would be the most informative primary diagnostic assessment?

- Blood sample to measure FSH, LH, estradiol, and testosterone
- Blood sample to measure FSH, LH, estradiol, testosterone, and AMH
- Karyotype analysis
- Family history

Answer: B) Blood sample to measure FSH, LH, estradiol, testosterone, and AMH

Case 1, Continued

Laboratory test results:

FSH = 17 mIU/mL (SI: 17 IU/L)
 LH = 45 mIU/mL (SI: 45 IU/L)
 Testosterone = 750 ng/dL (SI: 26 nmol/L)
 Estradiol = 25 pg/mL (SI: 92 pmol/L)
 AMH = 113 ng/mL (SI: 807 pmol/L)

The high testosterone value is not reflected in the physical signs. The AMH value within the male range confirms the presence of Sertoli cells.

In addition to referral to a multidisciplinary DSD team, which of the following blood tests are most appropriate from the clinical perspective?

- A. DSD gene panel
- B. Measurement of FSH, LH, estradiol, and testosterone
- C. Measurement of FSH, LH, estradiol, testosterone, and AMH and karyotype analysis
- D. Measurement of α -fetoprotein, hCG, and lactate dehydrogenase

Answer: A) DSD gene panel

It is important to verify the diagnosis of CAIS, as it underpins the next steps in the assessment. The diagnostic evaluation will be guided by the DSD team. The team will arrange contact with the psychologist, order ultrasonography or MRI of internal genitalia, and arrange for laparoscopy and gonadal biopsies, which includes experienced pathologist assessment with histological evaluation and staining for OCT3/4, TSPY, and KITLG.

Case 1, Continued

The assessment thus far does not indicate germ-cell neoplasia in situ. After shared decision-making, the patient decides to keep her gonads.

Which of the following is the best follow-up plan?

- A. No further follow-up with endocrinology, as no hormone treatment is needed
- B. Repeat biopsy after 10 years
- C. Self-assessment yearly
- D. Yearly follow-up at the endocrinology clinic with blood samples and MRI

Answer: D) Yearly follow-up at the endocrinology clinic with blood samples and MRI

The young woman continues to be followed up by the team. Blood tests for FSH, LH, estradiol, and testosterone are ordered to evaluate the hormonal situation. An annual hormone workup and MRI are recommended. A blood sample for analysis of α -fetoprotein, hCG, and lactate dehydrogenase may be considered, with the understanding that these tests are not elevated in neoplasia in situ. Another biopsy could be considered in 10 years.

Case 2

A 14-year-old boy seeks medical attention because he is very disturbed by gynecomastia. He is not active in sports and no longer goes to the gym. His height is 67.7 in (172 cm), and weight is 119 lb (54 kg) (BMI = 18.5 kg/m²). The first signs of puberty began about 1 year ago. Pubertal status is Ph3, and he has no acne. He has had hypospadias repair. Testicular volume is 6 cc. Gynecomastia corresponds to B3.

Which of the following investigations would be most informative?

- A. Measurement of FSH, LH, testosterone, and estradiol
- B. Measurement of FSH, LH, testosterone, and estradiol and karyotype analysis
- C. Genetic analysis of the AR gene
- D. Measurement of α -fetoprotein, hCG, and lactate dehydrogenase

Answer: B) Measurement of FSH, LH, testosterone, and estradiol and karyotype analysis

In this clinical situation, Klinefelter syndrome should be considered as a likely diagnosis.

Case 2, Continued

Laboratory test results:

FSH = 20 mIU/mL (SI: 20 IU/L)
 LH = 17 mIU/mL (SI: 17 IU/L)
 Testosterone = 404 ng/dL (SI: 14 nmol/L)
 Estradiol = 24 pg/mL (SI: 89 pmol/L)
 AMH = 32 ng/mL (SI: 229 pmol/L)
 Karyotype = 46,XY

Which of the following should be recommended first to address this patient's gynecomastia?

- A. Plastic surgery
- B. Testosterone (relatively high dosage)
- C. Aromatase inhibitor
- D. Dihydrotestosterone
- E. Psychological support

Answer: B) Testosterone (relatively high dosage)

Hormonal treatment with testosterone at a relatively high dosage can be tried. Topical application may be preferred because the dose can be easily adjusted. The biological effects of testosterone can be assessed by measuring FSH and, mainly, LH response. If the effect is insufficient, dihydrotestosterone (if available) or an aromatase inhibitor can be tried. An antiestrogen can also be tried. All treatment options should be discussed with the patient. If gynecomastia has developed over time, surgery is often required.

Case 3

A newborn is referred for evaluation because of uncertain sex assignment. The baby was born after an uneventful pregnancy in gestational week 39 with a birth weight of 3200 g. Apgar scores were 8, 9, and 10. On examination of the genitalia, there is no increased pigmentation, a gonad is possibly palpable on one side (1 ml/cc), the genital tubercle

measures 1.8 cm, there is a urethral opening at the base, and there is a bifid scrotum.

Which of the following is the most important next step?

- A. Gonadal ultrasonography
- B. Urgent referral to the DSD team
- C. Blood sample to analyze FSH, LH, estradiol, testosterone, and AMH
- D. Karyotype analysis
- E. Inform the family of the plan

Answer: B) Urgent referral to the DSD team

A multidisciplinary DSD team should guide the evaluation of this baby whose sex of rearing is uncertain. After meeting with the family, the team will plan and arrange hormonal and genetic investigations, explain the diagnostic steps, and ensure psychological support. The evaluation should include hormone assessment and genetic testing, including karyotype analysis to identify possible sex-chromosomal DSD and/or a gene panel. The hormone assessment should include testosterone as a marker of Leydig-cell function and AMH as a marker of Sertoli-cell function. These results are typically available more quickly than those from karyotype analysis. Clinical status and ultrasonography/MRI will clarify the location of the gonads and determine the presence of a uterus. A decision on the sex of rearing can then be made. The multidisciplinary DSD team will also plan follow-up for the child and family.

Key Learning Points

- The overall aim should be to optimize care related to different phases of life—neonatally, in adolescence, and throughout adult life—to improve quality of life, general health, and long-term outcomes.
- In cases of spontaneous puberty, follow-up should be done to ensure complete and normal pubertal development and a satisfactory hormonal status. If gonadectomized, puberty

treatment should be considered at age 11 years for girls and age 12 years for boys.

- Malignancy risk assessment with biopsies should be performed during late puberty. If the decision is made to retain the gonads, regular ultrasonography or MRI, along with self-examination, are essential for detecting the development of gonadal malignancy.
- Medical management with sex hormone replacement should be followed by clinical assessment, hormone testing, and safety monitoring. Regular lifelong follow-up should include blood pressure, cardiovascular and metabolic parameters, bone mineral density,

and psychological parameters to ensure appropriate management and care.

- Psychosocial support should be offered to all individuals with AIS. Patients should be involved in shared decision-making regarding gonads and hormone treatment.
- Transition from pediatric to adult care needs to be organized to ensure full disclosure and appropriate education about the aims and effects of hormone treatment, thereby optimizing future adherence. There is no evidence or general consensus on how often the different aspects of treatment and long-term effects should be followed up.

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THYROID BIOLOGY AND CANCER

Recent Advances in the Management of Anaplastic Thyroid Cancer

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe the necessary baseline testing to determine the best treatment of anaplastic thyroid cancer (ATC).
- Describe the optimal management of *BRAF* V600E-variant ATC.
- Describe the current management of non-*BRAF* V600E-variant ATC.

Significance of the Clinical Problem

ATC is the most aggressive type of thyroid cancer, with a historically short survival measured in months. This is due to the location of the rapidly growing mass, leading to airway compression resulting in asphyxiation, and to resistance to cytotoxic chemotherapy. Additionally, most patients are diagnosed when the tumor is too advanced to be meaningfully surgically resected, and approximately half of patients present with distant metastatic disease. Thus, historically, most patients were offered only palliative treatment and referral to hospice. However, recent advances in understanding the molecular drivers of ATC and in discovering effective management strategies have been game-changing. ATC management

is no longer focused on a single treatment or modality. Instead, patients are treated with a multistep approach using different modalities. The FAST (Facilitating Anaplastic Thyroid Cancer Specialized Treatment) multidisciplinary team has applied “Total Therapy,”¹ in ATC, although this approach is not typical for solid tumors.

Practice Gaps

Because ATC is rare, many physicians are unaware of the advances that have radically improved patient outcomes:

- Rapid determination of the *BRAF* V600E-variant status of ATC tumors.
- Comprehensive workup of ATC.
- Multistep (“Total Therapy”) management of localized and distant metastatic ATC.

Discussion

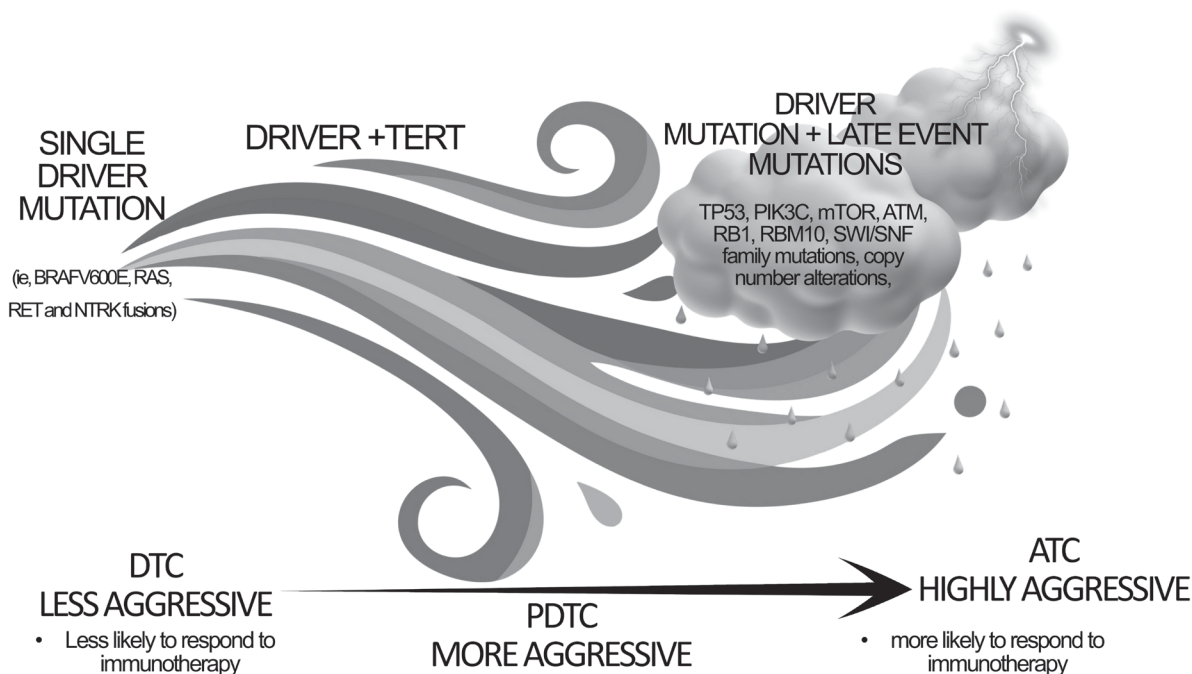
Our understanding of ATC has expanded rapidly in the past decades. We now know that these tumors emerge from well-differentiated thyroid cancers (DTC) and maintain the oncogenic driver alteration that caused the DTC. For example, the *BRAF* V600E variant is commonly seen in papillary thyroid cancer (PTC), and when these tumors gain late-event mutations in genes such as *TP53*, they become more aggressive cancers and can evolve into poorly differentiated thyroid cancer or ATC (Figure 1, following page). When these

tumors transform into highly aggressive cancers, they also express the protein programmed death-ligand 1 (PD-L1), which acts like a cloak, shielding the tumor from destruction by the patient's immune system.

Rapid Baseline Assessment: Staging and Determination of BRAF Status

Given the aggressive nature of ATC, once a diagnosis has been established or even suspected, a comprehensive staging evaluation should be performed (*Table 1*). ATC is considered a medical

Figure 1. Transformation of DTC to More Aggressive Thyroid Cancer (Poorly Differentiated and ATC)



The more aggressive forms of follicular-derived thyroid cancers are derived from DTC by acquiring late-event variants in genes such as *TP53*. These tumors also become more responsive to checkpoint inhibitor therapy as they transition to ATC. Abbreviations: DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer.

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Table 1. Initial Workup of Patients With ATC

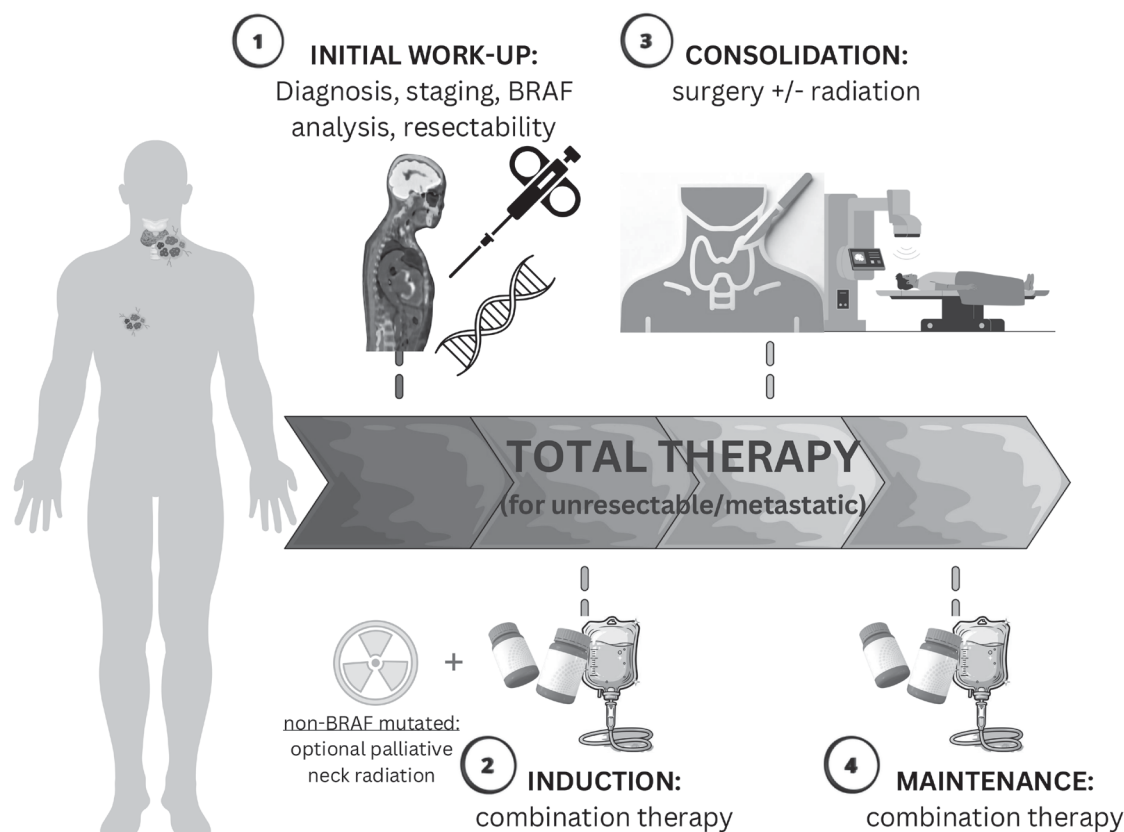
Biopsy	• Core biopsy or fine-needle aspiration with cell block • BRAF V600E with immunohistochemistry or rapid polymerase chain reaction • Liquid biopsy (optional) • Full next-generation sequencing • Pathology synonyms for tumors from the thyroid gland: poorly differentiated carcinoma, sarcomatoid, spindled, squamous carcinoma, undifferentiated
Staging	• MRI brain • CT neck, chest, abdomen, pelvis • ¹⁸F FDG PET-CT
Vocal cord/airway and swallowing assessment	• Laryngoscopy • Modified barium swallow

emergency, so this evaluation should be completed within 1 week. The staging evaluation serves to determine: (1) whether the primary tumor and locoregional disease are meaningfully resectable surgically, and (2) the extent of disease outside the neck. The American Joint Committee on Cancer (AJCC) staging² of ATC is straightforward:

- IVA = tumor confined to the thyroid gland (these are usually resectable and often found in retrospect after surgery).
- IVB = gross extrathyroidal extension and/or metastases to the locoregional lymph nodes, but no distant metastatic disease.
- IVC = distant metastatic disease.

While the patient undergoes staging examinations, the *BRAF* V600E-variant status must be rapidly determined by immunohistochemistry,^{3,4} single-gene polymerase chain reaction (PCR), or liquid biopsy.^{5,6} The first 2 tests require a biopsy but can provide results within days, while liquid biopsy (blood-based testing) may take up to 7 to 10 days. Once the staging and *BRAF* status are determined, the treatment plan can proceed, preferably after a discussion with a multidisciplinary team of surgeons, oncologic endocrinologists/medical oncologists, and radiation oncologists.

Figure 2. Total Therapy for Patients With Unresectable or Metastatic Disease



Patients with stage IVB unresectable or stage IVC disease should be fully staged and evaluated for the *BRAF* V600E variant (step 1). If the patient's tumor has the *BRAF* V600E variant, they should begin the Induction Phase (step 2) with dabrafenib/trametinib + pembrolizumab (when available). Patients without the *BRAF* V600E variant should be considered for Induction (step 2) with palliative radiation followed by lenvatinib/pembrolizumab. If the patient has a contraindication to lenvatinib, dual immunotherapy with ipilimumab/nivolumab can be considered. Restaging scans should be performed regularly (every 2 to 3 months) to determine if the patient is responding to therapy and to evaluate whether the primary tumor is resectable. In a patient with an excellent response throughout, removal of the primary tumor during the Consolidation Phase (step 3) could be considered within the first 6 months. Postoperative radiation should be discussed in a multidisciplinary forum, but this is often reserved for patients without metastatic disease, as targeted therapy is held during radiation. Finally, the Maintenance Phase (step 4) should be started soon after surgery ($\pm$ radiation). Patients who cannot undergo surgery may skip Consolidation and proceed directly to Maintenance (step 4), which consists of 1 to 2 years of PD-1 checkpoint inhibitor therapy, followed by indefinite continuation of the targeted therapy.

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Total Therapy Model

The Total Therapy model is similar to the principles of acute leukemia management, which are divided into treatment phases: Induction, Consolidation, and Maintenance Therapy (*Figure 2, preceding page*). In ATC, the Induction Phase involves rapid tumor cytoreduction and managing the emergence of resistant clones, which often occurs early in the disease course in most ATC patients. Consolidation is the second phase, during which good responses are typically achieved, usually with surgery to remove the primary tumor and/or radiation therapy. Surgical resection should only be pursued if the tumor can be fully removed, as leaving gross disease does not benefit patients and delays effective therapy. The final phase is Maintenance, during which patients are treated for extended periods to ensure the disease is fully eradicated or controlled.

Management of Surgically Resectable Disease

If surgery can achieve R0/R1 resection, patients without distant or oligometastatic disease should be considered for immediate surgical management. R0, R1, and R2 disease refer to the tumor status after surgery⁷:

- R0 = complete resection with clear margins
- R1 = microscopically positive margin
- R2 = gross residual disease (“debulking”)

We refer to the surgery based on what we believe the R status will be after reviewing the staging. Resectability depends on the involvement of

critical structures, including the larynx, trachea, esophagus, carotid artery or other great vessels, prevertebral fascia, recurrent laryngeal nerves, and mediastinum. Only surgeries that will result in an R0 or R1 classification should be performed, and only by an experienced thyroid cancer surgeon. Extensive resections involving total laryngectomy and esophagectomy carry a high risk of postoperative mortality and morbidity and result in poor quality of life. *Table 2* describes which patients should not undergo surgery, either because it would not be beneficial (no evidence indicating improved survival) or because the tumor is unresectable. The prognosis is unaffected by incomplete palliative resection (R2) or “debulking,” which is not recommended as an initial procedure.⁸ Since most patients are unable to undergo R0/R1 resections, we advocate treating upfront with systemic therapy and then evaluating for surgery in the Consolidation Phase.

Once surgery has been performed, external-beam radiation to the neck (up to 66 Gy) plus radiosensitizing chemotherapy should be initiated within 4 weeks. Radiosensitizing chemotherapy regimens, doses, and schedules can be found in society guidelines.^{9,10} Despite this aggressive treatment, patients often develop local recurrence or distant metastatic disease.¹¹ Adjuvant pembrolizumab, started within 4 to 6 weeks of completing hemoradiation, has been studied in a small trial.¹² Patients in this study were believed to have stage IVB disease after the completion of radiation. The study included 16 patients who received adjuvant pembrolizumab after completion of radiation. A retrospective cohort of patients observed without treatment

Table 2. Patients With ATC Who Should Not Undergo Surgery

Upfront surgery not usually advised	Unresectable
• Surgery that will leave gross disease behind • Bilateral recurrent laryngeal nerves at risk (may require tracheostomy) • Involves >4 cm trachea • Involves the larynx, pharynx (laryngectomy not advised) • Involves esophageal mucosa	• Encases carotid artery • Encases innominate artery • Involves prevertebral fascia, floor of the neck (R2 surgery and high morbidity) • Involves brachial plexus (high morbidity)

after radiation (age- and treatment-matched) was used as a historical control group. Most patients had undergone surgical resection. Patients in the adjuvant pembrolizumab arm did not reach a median progression-free (or overall) survival, while historical controls had a median progression-free survival and overall survival of 5.4 months (95% CI, 2.04-16.20; $P = .006$; hazard ratio, 0.24) and 31 months (95% CI, 13.9-NA; $P = .009$; hazard ratio, 0.11), respectively.

Management of BRAF V600E-Variant ATC

Induction Therapy (DTP)

For patients with *BRAF* V600E-variant ATC, which comprise 40% of ATC cases,^{13,14} the *BRAF*/MEK inhibitors dabrafenib and trametinib (DT) are FDA approved in the United States. This approval was based on a phase 2 trial showing response rates of 55% and a median overall survival of 14.5 months. When initiated promptly, these drugs^{5,16} can be used to cytoreduce tumors, providing for rapid symptom relief and eventually enabling resection of the primary tumor. Unfortunately, these responses are often short-lived, with resistant pathways emerging.¹⁷⁻¹⁹ Therefore, the Induction Phase consists of 2 steps: cytoreduction with DT, followed by strategies to prevent the emergence of resistance. In most of these tumors, both the ATC cells and the tumor immune microenvironment express PD-L1.²⁰⁻²² Thus, by targeting the immune system with an immune checkpoint inhibitor—pembrolizumab, which targets the PD-1/PD-L1 pathway—an attempt is made to deter resistance.²³⁻²⁵ Pembrolizumab should be added to DT therapy within 4 weeks. This combination, referred to as DTP, significantly improved median overall survival (17 months with DTP vs 9 months with DT, $P = .037$) and median progression-free survival (11 months with DTP vs 4 months with DT, $P = .049$) compared with DT alone.²⁴ The main limitation of this trial is that the data are retrospective. While pembrolizumab could be added at the time of progression, there is concern

that progression might be detected too late, by which time the patient's performance status has declined. Furthermore, a minority of patients do not exhibit a significant response to DT alone.¹⁶

Consolidation Therapy (Surgery ± Radiation)

Induction Therapy for *BRAF* V600E-variant ATC rarely achieves complete remission because of resistant clones or because the remaining thyroid tissue harbors more DTC (ie, PTC), which is less responsive to DT.²⁶⁻²⁸ Thus, the next step in ATC management is to consolidate good responses with surgery and/or radiation therapy. Both retrospective and prospective studies have shown that using neoadjuvant *BRAF*-directed therapy followed by surgical resection of the primary tumor has excellent outcomes,^{24,29,30} and this approach is now an accepted standard of practice where high-volume, complex thyroid surgeries are performed. A prospective, multicenter clinical trial with neoadjuvant DTP enrolled 40 patients, of whom 39 were evaluable. The primary endpoint was the gross surgical resection rate and overall survival. Surgeries had to be performed within 7 cycles of chemotherapy. The response rate was 72%, and the gross resection rate was 74% (R0/R1). The median overall survival was 18 months. Compared with a historical control, the study results were statistically significant. Interestingly, surgical pathology was a good biomarker for predicting outcomes, as those with a complete ATC pathologic response had significantly better overall survival than those with residual ATC in their surgical specimen. Patients who had completed surgery had the option to undergo postoperative radiation therapy to the neck with concurrent radiosensitizing chemotherapy to complete the consolidative treatment.

Maintenance Therapy (DTP)

Following Induction and Consolidation Therapy, patients should undergo an extended period of Maintenance Therapy with DTP. At this time, the recommendation is to administer pembrolizumab for a minimum of 1 year²⁵ and discontinue after 2 years, while DT is continued indefinitely.

Management of Non-*BRAF* V600E-Variant ATC With Distant Metastatic Disease

In the United States, *BRAF* testing and targeted treatment are readily available; however, this may not be the case in other countries. Furthermore, only 40% of ATC tumors harbor the *BRAF* V600E variant. Patients with non-*BRAF* V600E-variant ATC who do not have distant metastases should undergo surgery if feasible and/or receive external-beam radiation therapy with radiosensitizing chemotherapy, as described previously. The current standard of care for patients with non-*BRAF* V600E-variant ATC and distant metastatic disease is lenvatinib plus pembrolizumab. Although not FDA approved for ATC, this regimen has been included in the 2024 National Comprehensive Cancer Network guidelines.

Induction Therapy

To date, 3 clinical trials with lenvatinib and pembrolizumab have been reported.³¹⁻³³ A small retrospective trial of 6 patients was peer reviewed and published in 2021.³¹ Two prospective clinical trials have completed enrollment, one in the United States and the other in Europe (NCT04171622, EudraCT 2017-004570-3). Preliminary data from the European trial, presented in abstract form, showed an overall response rate of 55% and a median overall survival of 11 months.³² The US trial was a phase 2 clinical trial that recently completed enrollment.³³ Its primary endpoint was overall survival compared with a historical control. Twenty-five patients were enrolled, all of whom had distant metastatic disease at the time of study entry. The response rate was 36%, and the median overall survival was 11.4 months (95% CI, 7.8-35.6; $P < .025$). Notably, 96% of patients received local therapy to the neck—either surgery or radiation—before trial entry. This localized treatment is a major consideration before starting lenvatinib/pembrolizumab because the regimen has a lower response rate than DT, and patients often experience airway complications. Thus, radiation rapidly achieves control of the primary tumor but

may also prime the immune system to recognize tumor antigens.^{34,35}

Similar to the strategy for *BRAF* V600E-variant ATC, Consolidation Therapy with surgery for resectable tumors has been incorporated into the treatment regimen. This is followed by resuming lenvatinib plus pembrolizumab as Maintenance Therapy.

There are relative contraindications to lenvatinib, including large, unhealed wounds; hemoptysis; colitis; diverticulitis; intestinal perforation; recent bowel surgery; and tumors that invade the trachea or esophagus. Definite contraindications include a history of myocardial infarction within the past 6 months, uncontrolled hypertension, or poor cardiac function.³⁶ In these patients, another treatment consideration is the immune checkpoint inhibitor combination of ipilimumab (anti-CTLA4) plus nivolumab (anti-PD1).³⁷ Although it was a small study that included only 10 patients with ATC, the combination showed promising results, with a 30% objective response rate. Median overall survival was not reached.

Summary

The revolution in ATC treatment is the most significant therapeutic achievement in oncologic endocrinology this century. A better understanding of its molecular drivers and therapeutic vulnerabilities has expanded the range of available therapeutic interventions, allowing clinicians to offer treatment to patients who previously had minimal prospects for survival. The shift reflects steady progress in diagnostics, personalized therapy, and multidisciplinary care.

The multistep Total Therapy model has led to paradigm shifts in how we manage patients with ATC. Patients must be evaluated promptly for resectability and *BRAF* status to avoid treatment delays. We now know that it is not sufficient to treat patients who have active disease with targeted therapy alone. Instead, they should undergo Induction with combination therapy that includes immune checkpoint inhibitors, followed by Consolidation with surgery when feasible, and

then Maintenance Therapy with the drugs used during Induction to achieve longer survival.

Clinical Case Vignettes

Case 1

A man in his mid-60s with a history of lymphoma has a left paratracheal lymph node inferior to the left thyroid lobe identified on surveillance imaging. This has been observed for several years, but he has developed dysphagia and hoarseness, and undergoes CT of the neck and chest and a biopsy. Imaging shows the paratracheal mass without distant metastases, and pathology confirms ATC.

Which of the following tests would be the most helpful to determine treatment?

- A. *BRAF* by rapid method, such as immunohistochemistry or PCR
- B. *BRAF* by next-generation sequencing
- C. Liquid biopsy for 70 genes
- D. Gene expression profiling test to determine tumor origin
- E. Brain MRI

Answer: A) *BRAF* by rapid method, such as immunohistochemistry or PCR

Rapid determination of the *BRAF* V600E-variant status is a critical step in the initial workup, as it determines whether the patient is eligible for the FDA-approved, highly effective targeted DT therapy. While next-generation sequencing and liquid biopsy could be helpful (and next-generation sequencing should be sent on all patient tumors), these tests take longer to receive results. Brain MRI is part of the workup for ATC but is not the most helpful step for guiding treatment.

Case 1, Continued

Tumor immunohistochemistry for the *BRAF* V600E variant is positive, and the patient is enrolled in a study with neoadjuvant dabrafenib, 150 mg orally twice daily; trametinib, 2 mg

orally once daily; and pembrolizumab, 200 mg intravenously every 3 weeks. He experiences rapid symptom relief after 3 days. He has a partial response observed on month 2 imaging, and the tumor is deemed resectable. He undergoes a left thyroid lobectomy and central neck dissection. Surgical pathology documents thyroid parenchyma with chronic lymphocytic thyroiditis and no residual tumor. In the left neck central compartment neck dissection, metastatic PTC (0.6 cm) is found in 1 of 4 lymph nodes.

The patient undergoes radiation to the neck along with concomitant carboplatin and paclitaxel, during which time dabrafenib and trametinib are held. He completes radiation and resumes dabrafenib and trametinib 2 weeks later, then completes 2 years of pembrolizumab. There is no evidence of disease after 5 years.

Which of the following drugs are FDA approved for ATC in patients with the *BRAF* V600E variant?

- A. Lenvatinib
- B. Vemurafenib + cobimetinib
- C. Dabrafenib + trametinib
- D. Pembrolizumab
- E. Ipilimumab + nivolumab

Answer: C) *Dabrafenib + trametinib*

Dabrafenib and trametinib are the only FDA-approved drugs for ATC, but only for patients with the *BRAF* V600E variant.

Case 2

A woman in her mid-60s with ATC has a long history of thyroid nodules, for which she had a biopsy 30 years ago (she was told it was benign). Six months before ATC was diagnosed, she noticed a growing neck mass and underwent neck CT. This scan showed a 6.4-cm left thyroid mass invading the left wall of the trachea and abutting the carotid artery. Fine-needle aspiration confirmed ATC. Due to a COVID-19 infection, she was unable to return for follow-up for 4

weeks. By the time she is seen at our hospital, she is experiencing dyspnea, left neck/ear pain, dysphagia, and weight loss. A liquid biopsy fails to identify the *BRAF* V600E variant. The tumor is deemed unresectable, and radiation is recommended. She starts radiation with concomitant radiosensitizing chemotherapy with carboplatin plus paclitaxel. She develops liver toxicity and a pulmonary embolism and is then switched to cisplatin as the radiosensitizing chemotherapy. One month after completing 60 Gy of radiation, she starts adjuvant pembrolizumab, 400 mg intravenously every 6 weeks. She completes 2 years of pembrolizumab, after which time she is off all therapy. She remains disease-free 4 years later.

True or false? Patients with localized (stage IVB) ATC without the *BRAF* V600E variant should be treated with surgery if resectable, external-beam radiation, and radiosensitizing chemotherapy.

Answer: True

Patients with stage IVB ATC should be considered for complete surgical resection (R0/R1). After surgery, patients should proceed with external-beam radiation to the neck with radiosensitizing chemotherapy (chemoradiation). Those who cannot undergo surgery may skip this step and proceed to chemoradiation. A recent study also showed that adjuvant pembrolizumab after radiation improved overall survival in patients with stage IVB ATC.

Case 3

A woman in her early 70s started having a dry cough 4 months ago and noticed a right neck mass 1 month ago. She undergoes neck ultrasonography and core biopsy. The pathology is concerning for ATC, and she subsequently undergoes PET-CT. PET shows a large thyroid mass and a large lung mass.

True or false? All patients diagnosed with ATC should undergo full staging and rapid evaluation for *BRAF* V600E status by immunohistochemistry or rapid PCR test.

Answer: True

The initial workup for ATC includes staging, biopsy, and evaluation for the *BRAF* V600E variant. These steps should be accomplished simultaneously and within 1 week.

Case 3, Continued

Findings on biopsy of the large, right lower lung mass are consistent with ATC. Immunohistochemistry for the *BRAF* V600E variant is negative, and the tissue is sent for next-generation sequencing. She has an excellent performance status.

Following the Total Therapy model for ATC, which includes Induction, Consolidation, and Maintenance, which of the following is the best next therapeutic step?

- Start DTP therapy and then restage in 2 months to determine if her tumor is resectable
- Ask the surgeon to remove her large primary tumor and then administer chemoradiation followed by adjuvant pembrolizumab
- Evaluate the airway for stability and recommend palliative radiation followed by lenvatinib/pembrolizumab; restage in 2 months
- Start ipilimumab/nivolumab; restage in 2 months
- Discuss hospice with the patient

Answer: C) Evaluate the airway for stability and recommend palliative radiation followed by lenvatinib/pembrolizumab; restage in 2 months

After ensuring the airway is stable, palliative radiation (14-30 Gy over a short course) can be administered if this can be done rapidly. Lenvatinib/pembrolizumab is the most-studied Induction combination therapy for patients with non-*BRAF* V600E-variant ATC. Restaging

should be performed at regular intervals to assess treatment effectiveness and to consider Consolidation with surgery.

The patient received palliative radiation to the neck up to 15 Gy in 4 fractions and then started lenvatinib, 20 mg orally once daily, plus pembrolizumab, 400 mg intravenously every 6 weeks. Next-generation sequencing identified variants in the following genes: *NRAS* (Q61R), *PAX5*, *TERT* promoter, and *TP53*. The PD-L1 score was 30% by Tumor Proportion Score. After several cycles of lenvatinib/pembrolizumab, she had a partial response in the neck and lung and therefore underwent right lobectomy. Surgical pathology showed no ATC but did show partial viable well-differentiated thyroid follicles that were positive for *RAS* Q61 on immunohistochemistry.

Key Learning Points

- Rapid diagnosis, staging, and determination of *BRAF* V600E status are critical in the workup of all patients with ATC to guide appropriate therapy.
- The next critical step is to determine whether upfront complete surgical resection is possible. Patients with localized disease who can undergo R0/R1 surgery should proceed with surgery and external-beam radiation, with consideration for adjuvant pembrolizumab.
- In patients who cannot undergo complete surgical resection or who have distant metastatic disease, combination therapy with matched targeted therapy (ie, *BRAF* V600E variant → dabrafenib/trametinib; non-*BRAF* V600E variant → lenvatinib) plus an immune checkpoint inhibitor or dual checkpoint inhibitor is the first step in Induction Therapy for ATC.
- Consolidation Therapy with surgical resection of the primary tumor ± radiation should be considered before the seventh cycle of Induction Therapy.
- Maintenance Therapy with the drugs used during Induction is necessary after Consolidation Therapy.

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Evaluation and Management of Thyroid Dysfunction in Pregnancy

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the appropriate diagnostic criteria for thyroid dysfunction during pregnancy, given physiological changes that affect thyroid hormone production.
- Explain the potential adverse effects of overt thyroid dysfunction on obstetric and offspring outcomes.
- Differentiate among the different causes of hyperthyroidism and the appropriate management strategies.
- Formulate appropriate management plans for hyperthyroidism during pregnancy, taking into account the treatment threshold and the potential effects that different treatment modalities could have on the fetus.
- Review considerations for managing subclinical hypothyroidism in pregnancy.
- Formulate management plans for subclinical hypothyroidism during pregnancy, balancing potential benefits and risks.

Significance of the Clinical Problem

Adequate thyroid hormone is critical for normal fetal development. Maternal thyroid dysfunction during pregnancy can adversely affect obstetric and offspring outcomes. Thyroid disease is the

most common endocrine disorder in young women and is more prevalent in women than in men. Hypothyroidism is estimated to affect 4% of pregnancies (0.5% overt and 3.5% subclinical), and hyperthyroidism is estimated to affect 2.4% of pregnancies (0.6% overt and 1.8% subclinical). Because the fetal thyroid gland does not form until 8 to 10 weeks' gestation and does not produce a meaningful amount of thyroid hormone until 18 to 20 weeks' gestation, the fetus depends entirely on maternal thyroid hormone crossing the placenta during the critical first trimester. Both overt hyperthyroidism and overt hypothyroidism in pregnant women have been shown to increase the risk of adverse pregnancy outcomes. Untreated severe maternal hyperthyroidism during pregnancy is associated with increased risks of pregnancy-induced hypertension, pregnancy loss, maternal and fetal congestive heart failure, intrauterine growth retardation, low birthweight, and fetal/neonatal hyperthyroidism. Untreated severe maternal hypothyroidism in pregnancy is associated with increased risks of preterm birth, pregnancy loss, pregnancy-induced hypertension, placental abruption, and postpartum hemorrhage in mothers, as well as low birthweight and respiratory distress syndrome in offspring. Thyroid hormone is also essential for fetal brain development, playing an important role in neuronal migration and connectivity, myelination, and synaptogenesis. A seminal study by Haddow and colleagues in 1999 showed that children born to mothers with hypothyroidism in pregnancy had a 4-point lower IQ than children born to euthyroid mothers when assessed between

7 and 9 years of age. The difference in children's IQ was even higher (7 points) when a subset of mother-child pairs from untreated hypothyroid mothers was evaluated. Thus, the adverse effects of untreated severe overt thyroid dysfunction in pregnancy are well-established. However, studies show conflicting results regarding the effects and treatment benefits of subclinical thyroid dysfunction in pregnancy. Given this uncertainty, the approach to screening for thyroid function in pregnancy is also debated.

Practice Gaps

- Pregnancy- and trimester-specific thyroid function reference ranges are unavailable in most clinical settings.
- There is uncertainty about the optimal treatment options for maternal hyperthyroidism in early pregnancy, given the potential adverse effects of currently available antithyroid drugs.
- There is a lack of evidence from currently available trials regarding the clear benefits of levothyroxine treatment of subclinical hypothyroidism in pregnancy in mitigating adverse effects.
- There is a lack of large randomized clinical trials assessing the effects of subclinical hypothyroidism and the benefits of treatment in early pregnancy.

Discussion

Thyroid Function Testing in Pregnancy

Thyroid hormone requirements increase during pregnancy due to several factors, including (1) the need to support the developing fetus, especially in early pregnancy, (2) increased thyroxine-binding globulin (TBG) from high estrogen, leading to decreased free T_4 levels, and (3) increased inactivation of T_4 to reverse T_3 (rT_3) by type 3 deiodinase in placental and fetal tissues. To

meet this increased demand, thyroid hormone production rises during early pregnancy. hCG produced during pregnancy also has weakly thyrotropic effects. These physiological changes lead to a slight leftward shift in the distribution of serum TSH in early pregnancy compared with prepregnancy levels.¹⁰ Serum TSH measurement remains the best test for assessing maternal thyroid function during pregnancy. Ideally, assay- and trimester-specific reference ranges should be used to assess gestational thyroid function. However, such reference ranges are frequently unavailable. When trimester-specific reference ranges are unavailable, both the American Thyroid Association (ATA) and the American College of Obstetricians and Gynecologists (ACOG) recommend using slightly lower reference ranges for TSH, between 0.1 and 4 mIU/L, especially in the first trimester.^{11,12} Free T_4 measurement is used to assess the degree of thyroid dysfunction. Because TBG levels increase during pregnancy, indirect immunoassays for free T_4 may be inaccurate and yield falsely low free T_4 levels, especially in the second half of pregnancy.¹ Total T_4 or total T_3 levels can serve as surrogate markers of thyroid function. To account for increased TBG, the upper limit of normal ranges for total T_4 or total T_3 can be calculated by adding 5% per week of gestation between 7 and 16 weeks' gestation and by using 150% of the upper limit of normal after 16 weeks' gestation, when the increase in TBG stabilizes.¹¹

Hyperthyroidism in Pregnancy

Untreated severe hyperthyroidism in pregnancy can adversely affect maternal and fetal health. However, not all hyperthyroidism in pregnancy requires treatment. The most common cause of hyperthyroidism in pregnancy is gestational transient thyrotoxicosis (GTT), which is estimated to occur in 2% to 11% of pregnancies, depending on the region and population.^{13,14} GTT is mediated by the thyrotropic effect of hCG and occurs in the presence of very high hCG levels, such as in hyperemesis gravidarum. GTT is transient and

resolves spontaneously in the second trimester as hCG levels decrease. GTT is not associated with adverse pregnancy outcomes and does not require treatment with antithyroid drugs (ATDs). Patients with GTT can be treated supportively for nausea and vomiting associated with high hCG levels and/or with pregnancy-safe β -adrenergic blockers, such as metoprolol, for palpitations and tachycardia.

The second most common cause of hyperthyroidism in pregnancy is Graves disease, an autoimmune thyroid disease caused by stimulating TRAb. The prevalence of Graves disease in pregnancy is estimated at 0.2%. Severe, untreated Graves disease can lead to adverse pregnancy outcomes, and treatment is warranted based on severity. Because GTT and Graves disease affect pregnancy outcomes differently and require distinct treatment, it is important to differentiate between these conditions. The *Table* lists the characteristics of GTT and Graves disease.

To distinguish between GTT and Graves disease, pregnant patients with hyperthyroidism should have serum TRAb or thyroid-stimulating immunoglobulin (TSI) measured. Thyroid ultrasonography is not helpful in distinguishing GTT from Graves disease. A radionuclide thyroid scan is contraindicated during pregnancy. If the TRAb titer is negative, patients may be monitored with repeat thyroid function tests every 2 to 4 weeks until resolution or progression without ATD treatment. If the TRAb titer is positive, patients may require treatment for Graves disease depending on the severity. As radioactive

iodine ablation is contraindicated in pregnancy, ATDs, including methimazole (MMI) and propylthiouracil (PTU), are the primary treatment options. Both MMI and PTU are associated with increased risks of congenital malformation when used in pregnancy, although the risk is higher with MMI than with PTU. A large Korean study found an increased risk of congenital malformation among those exposed to PTU only (7.0%), MMI only (8.1%), or both PTU and MMI (8.0%), compared with the unexposed (5.9%).¹⁶ Similarly, a Danish study showed increased risks of congenital malformation among those exposed to PTU only (8.0%), MMI only (9.1%), or both PTU and MMI (10.1%) compared with the unexposed (5.7%).¹⁷ Exposure to MMI is also associated with more severe congenital malformations, such as aplasia cutis, esophageal or choanal atresia, or ventricular septal defects, whereas PTU is associated with relatively less severe congenital malformations, such as cysts or sinuses in the face and neck, or hydronephrosis.¹⁸ If a patient was treated with ATDs for Graves disease before pregnancy, discontinuation of the drug in early pregnancy may be considered to minimize exposure during the critical period of development. Good candidates may be patients who have been treated with ATDs for more than 6 months, have a normal TSH concentration on a small ATD dosage (eg, MMI <10 mg daily or PTU <200 mg daily), and have a low TRAb concentration (<3 times the upper normal limit).¹¹ If ATDs are needed in pregnancy, PTU is preferred over MMI due to a lower risk of congenital malformation and a less

Table. Characteristics of GTT and Graves Disease in Pregnancy

Characteristics	GTT	Graves disease
Nausea/vomiting	Severe	Usually absent
Presence of TRAb	No	Yes
Stigmata of Graves disease	None	May have diffuse goiter and Graves ophthalmopathy on exam
Thyroid function tests at diagnosis	T ₃ :T ₄ ratio frequently <20	T ₃ :T ₄ ratio is frequently >20
Thyroid function tests progression	Generally improves and normalizes in the second trimester	Generally remains low and may worsen

severe form of congenital malformation until 16 weeks' gestation. If a patient is taking MMI at the time of evaluation, switching to PTU can be considered depending on the time of presentation, as exposure to both MMI and PTU in pregnancy confers a similar risk of congenital malformation as MMI alone.^{16,17}

Most patients on both MMI and PTU were likely switched from MMI to PTU later in the first trimester, and the effects of MMI exposure may already have been present by then. Therefore, it may be reasonable to switch from MMI to PTU very early in gestation, but switching closer to the end of the first trimester may not significantly decrease the risk of congenital malformation and may result in suboptimal control of hyperthyroidism (new 2026 ATA guidelines under review). If needed, an MMI-to-PTU dose ratio of 1:20 can be used for conversion. A "block and replace" regimen with high-dosage ATDs and concurrent levothyroxine is generally not recommended, as ATDs can cross the placenta and cause fetal thyroid dysfunction. Thyroid function while on ATDs should be closely monitored every 4 weeks, and the free T₄ level should be kept in the upper one-third or just above the normal reference range to ensure adequate thyroid hormone availability to the fetus (new 2026 ATA guidelines under review), as normal maternal thyroid function on ATDs may indicate fetal hypothyroidism.¹⁹

Maternal subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes.²⁰⁻²³ Thyroid autoimmunity generally decreases in the late second to third trimester due to pregnancy-induced immune tolerance,²⁴ and 20% to 30% of patients with Graves disease treated with ATDs may be able to discontinue treatment. All pregnant patients with a history of Graves disease should have serum TSH and TRAb (or TSI) levels measured in the first trimester, especially if they have a history of definitive therapy. TRAb levels can increase acutely after radioactive iodine ablation and remain elevated for several years afterward.²⁵ TRAb levels decrease more rapidly after ATD treatment or

thyroidectomy. TRAb crosses the placenta in small amounts, and high maternal TRAb levels in pregnancy can increase the risk of fetal or neonatal hyperthyroidism and goiter. Women with a history of Graves disease or those who are actively treated with ATDs should have TRAb levels measured in the first trimester. If the TRAb level is more than 3 times the upper normal limit in the first trimester, the TRAb titer should be rechecked at 18 to 22 weeks' gestation to assess the risk of fetal hyperthyroidism, and again at 30 to 34 weeks' gestation to assess the risk of neonatal hyperthyroidism. If TRAb levels fall below 3 times the upper normal limit at any point in pregnancy, they do not need to be rechecked again (new 2026 ATA guidelines under review).

Hypothyroidism in Pregnancy

The adverse effects of untreated overt hypothyroidism and the increased thyroid hormone requirements have been reviewed in previous sections of this chapter. Levothyroxine monotherapy is the preferred treatment for hypothyroidism in pregnancy.¹¹ Liothyronine or desiccated thyroid extracts are not recommended during pregnancy because they do not cross the fetal blood-brain barrier. Even when maternal thyroid function is normal on liothyronine or on a combination of liothyronine and levothyroxine, the fetus may not have adequate thyroid hormone levels for proper neurodevelopment. The levothyroxine requirement increases by 20% to 30% in early pregnancy, and patients should be counseled to empirically increase their levothyroxine dose once they become pregnant. The TSH goal for pregnant patients treated with levothyroxine is less than 2.5 mIU/L. Serum TSH should be monitored every 4 weeks during the first half of pregnancy and at least once in the third trimester. Serum TSH should also be rechecked 4 to 6 weeks after the levothyroxine dose adjustment. Patients can resume their prepregnancy levothyroxine dose immediately after delivery.

Unlike overt hypothyroidism, the potential adverse effects and the need for treatment of maternal subclinical hypothyroidism are less clear. Most studies on this topic are cohort studies with conflicting results, although there is increasing evidence of an association between maternal subclinical hypothyroidism and risks of pregnancy loss and preterm delivery.^{22,23,26-28} These conflicting results may be due to variability among studies in the timing of TSH measurements, the TSH cutoff used to classify subclinical hypothyroidism, and TPO-antibody measurements. The lack of clear benefits of levothyroxine in improving pregnancy outcomes in the current literature also makes it difficult to strongly recommend treating maternal subclinical hypothyroidism in pregnancy. Although smaller Iranian studies showed decreased risk of preterm delivery with levothyroxine treatment of maternal subclinical hypothyroidism, especially if the TSH concentration is greater than 4 mIU/L,^{29,30} a larger US study did not show any benefit of levothyroxine treatment of maternal subclinical hypothyroidism on adverse pregnancy outcomes.³¹ None of the currently available clinical trials have shown that levothyroxine treatment of maternal subclinical hypothyroidism significantly benefits offspring neurodevelopment.³¹⁻³⁴ The biggest limitation of these studies is that patients were started on levothyroxine at 11 to 17 weeks' gestation, which may limit the potential benefit of treatment since early pregnancy is the critical period of development. A Danish study of 1981 mother-child pairs showed that both low and high maternal TSH levels were associated with lower grey matter volume in children at approximately 10 years of age.³⁵ Interestingly, this association was observed only with maternal TSH measured at 8 to 12 weeks' gestation, but not with levels beyond 12 weeks' gestation. A United Kingdom clinical trial reported no significant effect of levothyroxine treatment of maternal subclinical hypothyroidism starting at 12 to 13 weeks' gestation on children's brain volume at 10 to 16 years of age.³⁶ These findings suggest that there is a critical period of intervention for maternal thyroid dysfunction, namely in early pregnancy. Another limitation of

these studies is the use of levothyroxine dosages ranging from 100 mcg daily, 150 mcg daily, to 1 mcg/kg per day, which might have led to overtreatment and blunting of beneficial effects.

It should also be noted that a single abnormal thyroid function test may not indicate persistent thyroid dysfunction. A large Chinese study found that only 24.8% of subclinical hypothyroidism diagnosed between 9 and 14 weeks' gestation was persistent on repeat testing at 32 to 36 weeks' gestation.³⁷ A Danish study showed that only about 40% to 50% of mild TSH abnormalities (0.2 mIU/L < TSH < 6 mIU/L) noted between 9 and 14 weeks' gestation were persistent when reassessed at 12 to 15 weeks' gestation.³⁸ Based on this evidence, the upcoming 2026 ATA Thyroid and Pregnancy guidelines recommend either rechecking TSH or starting levothyroxine based on individual preference and risk factors if TSH is less than 6 mIU/L for overt hyperthyroidism, and to consider levothyroxine only if subclinical hypothyroidism is diagnosed in the first trimester (new 2026 ATA guidelines under review). Given the lack of clear clinical benefits of levothyroxine treatment for subclinical hypothyroidism beyond early pregnancy, patients diagnosed with subclinical hypothyroidism in the second or third trimesters can be monitored with repeat TSH measurements (new 2026 ATA guidelines under review).

Thyroid Autoimmunity in Pregnancy

Thyroid autoimmunity is the second most common cause of hypothyroidism in non-iodine-deficient regions. Because thyroid autoimmunity greatly increases the risk of hypothyroidism, especially during pregnancy,³⁹ the potential effects of thyroid autoimmunity on pregnancy outcomes have been studied. Meta-analyses have shown an association between maternal thyroid autoimmunity during pregnancy and increased risks of adverse outcomes, such as pregnancy loss⁴⁰ or preterm delivery.²² Although a smaller study reported lower risks of miscarriage and preterm delivery in euthyroid women with positive TPO antibodies treated with levothyroxine than in

those who were not treated,⁴¹ larger clinical trials have not shown any significant benefit of levothyroxine treatment for euthyroid women with positive TPO antibodies in mitigating risks of adverse pregnancy outcomes.⁴²⁻⁴⁴ Based on the available data, the upcoming 2026 ATA thyroid and pregnancy guidelines do not recommend levothyroxine treatment for euthyroid pregnant women with positive TPO- or thyroglobulin-antibody titers.

Screening for Thyroid Dysfunction in Pregnancy

There is no clear consensus on screening for thyroid dysfunction during pregnancy. The 2017 ATA guidelines and the 2014 European Thyroid Association guidelines state that there is insufficient evidence to recommend universal screening for thyroid dysfunction to detect subclinical disease.^{11,45} In contrast, ACOG and the American Society of Reproductive Medicine both recommend against universal screening for thyroid dysfunction in pregnancy.^{12,46} The current 2017 ATA guidelines recommend a case-finding approach based on a long list of risk factors, including known thyroid autoimmunity, age older than 30 years, history of other autoimmune diseases, family history of autoimmune diseases, obesity, multiparity, history of pregnancy loss, preterm delivery, or infertility, living in an area of iodine deficiency, and history or symptoms of thyroid dysfunction.¹¹ Many pregnant women would be considered at risk based on this list. An individual participant data meta-analysis, including more than 65,000 patients from 25 cohorts worldwide, was conducted to assess the clinically meaningful effect of each proposed risk factor.³⁹ The absolute risk increase was small for most risk factors, although all were associated with an increased risk of maternal thyroid dysfunction. Therefore, it is unclear whether these risk factors confer benefit for targeted screening. The presence of thyroid autoimmunity, especially positive TPO-antibody titers, was clearly associated with a significantly increased risk of thyroid dysfunction

and provided a strong indication for treatment. Based on this finding, the upcoming 2026 ATA thyroid and pregnancy guidelines recommend a graded approach to the frequency and timing of thyroid screening. Universal screening of thyroid dysfunction in pregnancy is still not recommended.

Clinical Case Vignettes

Case 1

A 32-year-old pregnant woman is referred for evaluation of abnormal thyroid function test results. She has no relevant medical history. This is her first pregnancy, and she is currently at 6 weeks' gestation.

Thyroid function test results:

TSH = <0.01 mIU/L (nonpregnancy reference range, 0.35-4.9 mIU/L)
 Free T₄ = 1.72 ng/mL (nonpregnancy reference range, 0.8-1.6 ng/dL) (SI: 22.14 pmol/L [10.30-20.59 pmol/L])
 Total T₃ = 260 ng/dL (nonpregnancy reference range, 83-160 ng/dL) (SI: 4.00 nmol/L [1.28-2.46 nmol/L])
 TSI = 480% (<140%)

Which of the following is NOT recommended for managing this patient's hyperthyroidism in pregnancy?

- A. Start PTU at a low dosage
- B. Do not start any antithyroid medication now; repeat thyroid function tests in 2 to 4 weeks
- C. Recheck serum TSI level at 18-20 weeks' gestation
- D. If the patient is being treated with an ATD, the goal free T₄ level should be in the mid-normal range

Answer: D) If the patient is being treated with an ATD, the goal free T₄ level should be in the mid-normal range

This patient has hyperthyroidism with mild elevations of free T₄ and total T₃ (both just above the normal range, with 5% per gestational week added to the upper normal limit for

total T_3) due to Graves disease (elevated TSI). Given that the free T_4 and total T_3 levels are just above the normal range, either starting ATDs (PTU preferred, given early gestation) or close monitoring of thyroid function would be reasonable. Since the first-trimester TSI level is elevated to more than 3 times the upper normal limit, it should be rechecked later in gestation to assess for the risk of fetal hyperthyroidism. Because ATDs cross the placenta, the goal free T_4 level in pregnant women treated with ATDs for hyperthyroidism is in the upper one-third to just above the upper limit of the reference range.

Case 2

A 30-year-old pregnant woman is referred for evaluation of abnormal thyroid function test results. She is currently at 10 weeks' gestation, and this is her first pregnancy. She has been experiencing fatigue and constipation.

Thyroid function test results:

TSH = 6.0 mIU/L (nonpregnancy reference range, 0.35-4.9 mIU/L)
Free T_4 = 1.2 ng/dL (nonpregnancy reference range, 0.8-1.6 ng/dL) (SI: 15.44 pmol/L [10.30-20.59 pmol/L])

What is NOT an appropriate next step?

- A. Start low-dosage levothyroxine
- B. Start low-dosage desiccated thyroid extract
- C. Repeat thyroid function tests in 2 weeks
- D. Check TPO-antibody titers

Answer: B) Start low-dosage desiccated thyroid extract

This patient has subclinical hypothyroidism with a slight TSH elevation. Although several studies have linked maternal subclinical hypothyroidism to adverse obstetric outcomes, currently available clinical trials do not show a clear benefit of levothyroxine treatment. A study also found that 40% to 50% of subclinical hypothyroidism spontaneously resolves on repeat check. She is in her first trimester, when levothyroxine treatment may still confer benefit for fetal development.

Therefore, either starting low-dosage levothyroxine or rechecking thyroid function tests in 2 to 4 weeks would be a reasonable next step. One could also check TPO-antibody titers to assess the risk of worsening thyroid function, although the presence of TPO antibodies would not affect the decision to treat with levothyroxine per the upcoming 2026 ATA thyroid and pregnancy guidelines. TPO-antibody status may provide additional information regarding the need for further monitoring during pregnancy. Desiccated thyroid extract or a combination of T_4 and T_3 is not recommended in pregnancy.

Case 3

A 30-year-old woman is referred for evaluation of abnormal thyroid function test results. Her primary care doctor ordered testing because she has been tired. Her mother has hypothyroidism due to Hashimoto thyroiditis. The patient has never been pregnant but is actively trying to conceive.

Thyroid function test results:

TSH = 3.5 mIU/L (0.35-4.9 mIU/L)
TPO antibodies = 230 IU/mL (<5 IU/mL)

Which of the following is an appropriate counseling/recommendation for this patient regarding her thyroid status and pregnancy planning?

- A. She should start low-dosage levothyroxine to keep TSH <2.5 mIU/L
- B. Treating thyroid autoimmunity before conception will decrease risks of adverse pregnancy outcomes such as miscarriage or preterm delivery
- C. She should have her TSH monitored at the beginning of pregnancy and periodically throughout gestation
- D. Presence of high TPO-antibody titer does not increase risk of developing thyroid dysfunction in pregnancy because her TSH is currently normal

Answer: C) She should have her TSH monitored at the beginning of pregnancy and periodically throughout gestation

Although thyroid autoimmunity, especially elevated TPO-antibody titers, increases the risk of thyroid dysfunction during pregnancy, there is no clear benefit of levothyroxine treatment for euthyroid TPO antibody-positive women before or during pregnancy in reducing the risk of adverse effects on pregnancy outcomes or children's neurodevelopment. However, because TPO-antibody positivity increases the risk of thyroid dysfunction during pregnancy, serum TSH should be monitored periodically, starting in early pregnancy.

Key Learning Points

- The TSH reference range shifts leftward during pregnancy. Ideally, assay- and pregnancy-specific TSH ranges should be used. If unavailable, $0.1 \text{ mIU/L} < \text{TSH} < 4 \text{ mIU/L}$ can be used during pregnancy.
- Free T_4 levels may be inaccurate during pregnancy due to increased TBG. Total T_4 or total T_3 levels, corrected for TBG, can be used to assess the degree of thyroid dysfunction or to set a treatment goal for hyperthyroidism during pregnancy.
- GTT and Graves disease should be differentiated as the cause of hyperthyroidism in early pregnancy because they are treated differently.
- PTU is associated with a lower risk of less severe congenital malformations than MMI, so PTU is preferred for the treatment of hyperthyroidism in pregnancy when indicated before 16 weeks' gestation.
- In patients with hyperthyroidism treated with ATDs, the goal free T_4 level is in the upper one-third or just above the upper limit of normal to avoid fetal hypothyroidism.
- If maternal TRAb or TSI levels are more than 3 times the upper limit of normal in the first trimester, they should be rechecked at 18 to 22 weeks' gestation and at 30 to 34 weeks' gestation.
- Levothyroxine monotherapy is the treatment of choice for hypothyroidism in pregnancy, with the goal TSH concentration less than 2.5 mIU/L .
- Patients with mild TSH elevation can be monitored with repeat TSH measurements through shared decision-making.
- Treatment of subclinical hypothyroidism depends on the timing of diagnosis rather than the presence of thyroid autoimmunity (eg, TPO-antibody status).
- Treating euthyroid patients with thyroid autoimmunity (eg, positive TPO-antibody titers) with levothyroxine is not recommended.

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Novel Insights in the Treatment of Hyperthyroidism

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the different treatment options for patients with hyperthyroidism.
- Incorporate different treatment options for hyperthyroidism in clinical decision-making for individual patients (personalized medicine).
- Review novel potential treatment modalities for hyperthyroidism.

Significance of the Clinical Problem

Untreated thyrotoxicosis is associated with substantial morbidity, including impaired quality of life and increased risk of cardiovascular complications and all-cause mortality.¹ Selection of the most appropriate therapeutic strategy is primarily determined by the underlying cause, with Graves disease, toxic nodular goiter, and thyroiditis representing the most common etiologies of overt thyrotoxicosis. In addition, the incidence of drug-induced thyrotoxicosis has risen in recent years, largely due to the expanding use of newer pharmacological agents, such as immune checkpoint inhibitors, tyrosine kinase inhibitors, and targeted monoclonal antibody therapies.² The article by Barroso-Sousa et al is an excellent review on the incidence of endocrine dysfunction after the use of immune checkpoint inhibitors.³

By definition, thyrotoxicosis describes the clinical state resulting from excessive thyroid

hormone action at the tissue level, whereas hyperthyroidism specifically refers to disorders characterized by increased synthesis and secretion of thyroid hormones by the thyroid gland. Despite this conceptual distinction, both terms are often used interchangeably in everyday clinical practice.

Therapeutic decision-making for patients with thyrotoxicosis caused by hyperthyroidism is guided by the underlying pathophysiological mechanism, with antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and thyroidectomy constituting the main treatment modalities.^{4,5} In Europe and the Asia-Pacific region, ATDs are generally considered the preferred first-line treatment for Graves disease. In contrast, treatment patterns in the United States have shifted over the past 2 decades, with a growing preference for ATDs over RAI.² Emerging data supporting the efficacy and safety of prolonged low-dosage ATD therapy in Graves disease are likely to further influence future treatment paradigms.⁶

After establishing the diagnosis, optimal management is influenced not only by etiology but also by disease severity and phase, as well as individual patient characteristics, including age, sex, and the presence of comorbid conditions. While biochemical confirmation of thyrotoxicosis is usually straightforward, diagnostic uncertainty may arise in specific situations, such as analytical interference or less common causes, including TSH-secreting pituitary adenomas or iatrogenic hyperthyroidism. This chapter will focus on recent advances and emerging concepts in the treatment of hyperthyroidism. For a detailed discussion of diagnostic pitfalls and rare etiologies, the reader is referred to my *Meet the Professor*

chapter coauthored with Dr. Chaker, presented at ENDO 2024.⁷

Practice Gaps

- Limited availability of large-scale randomized controlled trials that directly compare clinical outcomes among the various therapeutic approaches across distinct categories of hyperthyroid disease.
- Marked variability in treatment preferences among physicians in different regions worldwide.
- Insufficient awareness that all established treatment options for hyperthyroidism may each be considered as an initial therapeutic strategy, depending on disease etiology, disease severity, and individual patient preferences, as well as therapeutic strategy in patients with recurrence.
- Persistent uncertainty regarding the most appropriate management of hyperthyroidism in patients with a desire for pregnancy requires careful consideration for both maternal and fetal thyroid physiology.

Discussion

Diagnosis of Hyperthyroidism

Overt thyrotoxicosis is biochemically defined by a suppressed serum TSH concentration, typically below 0.01 mIU/L, in conjunction with elevated serum free T_4 and/or increased total or free T_3 levels. For an in-depth discussion of diagnostic strategies and therapeutic approaches in hyperthyroidism, the reader is referred to the article by Chaker et al.¹ Measurement of free T_4 , which reflects the biologically active unbound hormone fraction, is preferred over total T_4 assessment. Owing to the methodological limitations of currently available free T_3 assays, determining either total or free T_3 is acceptable. In most clinical settings, laboratory confirmation of thyrotoxicosis is uncomplicated, although

several conditions that are beyond the scope of this chapter may give rise to diagnostic uncertainty.⁷

In the setting of biochemical hyperthyroidism, assessment of TRAb represents a cornerstone in the diagnostic workup. Widely used immunoassays detect TRAb without distinguishing between thyroid-stimulating antibodies (TSI) and thyroid-blocking antibodies, both of which may coexist in individual patients. This lack of functional differentiation can complicate interpretation in selected clinical scenarios. More recently, automated bridge-based binding assays have been introduced that preferentially, although not exclusively, detect TSI.⁸ In general patient populations, both conventional TRAb immunoassays and newer TSI-focused assays demonstrate high diagnostic sensitivity and specificity.

When the etiology of thyrotoxicosis cannot be readily established from clinical and biochemical findings, thyroid scintigraphy is a valuable diagnostic adjunct. In Graves disease, diffuse and homogeneous radiotracer uptake, such as ^{123}I , ^{131}I , or $^{99\text{m}}\text{Tc}$, is observed, typically with elevated or high-normal uptake values. In contrast, tracer uptake is usually markedly reduced or absent in all forms of thyroiditis and in iodine-induced hyperthyroidism, reflecting suppressed tracer uptake due to iodine excess. In toxic nodular goiter, scintigraphy characteristically reveals focal areas of increased and decreased tracer accumulation, corresponding to so-called hot and cold nodules.

Thyroid ultrasonography is indicated when nodules are detected on physical examination or when scintigraphy identifies cold nodules requiring further evaluation. In centers where thyroid scintigraphy is unavailable, ultrasonography with color-flow Doppler may be used to assess thyroid vascularity and differentiate Graves disease from other causes of thyrotoxicosis. Increased thyroidal blood flow is typically observed in Graves disease, whereas vascularity is normal or reduced in most forms of thyroiditis. A notable limitation of this approach is the increased likelihood of detecting incidental thyroid nodules,

which may lead to overdiagnosis and subsequent identification of clinically insignificant nodules or microcarcinomas.⁹

Different Treatment Strategies for Hyperthyroidism

The selection of an appropriate therapeutic approach in patients with hyperthyroidism is mainly determined by the underlying pathophysiological mechanism, but disease severity and patient age are also factors that should be taken into account. The 3 principal treatment modalities are ATDs, RAI therapy, and thyroidectomy. In patients presenting with cardiovascular symptoms—most notably palpitations— β -adrenergic blockade can be initiated as symptom treatment, irrespective of the etiology of hyperthyroidism.

Toxic Adenoma or Toxic Nodular Goiter

For patients with a toxic adenoma or toxic multinodular goiter, RAI therapy and surgical intervention have traditionally been regarded as the preferred definitive treatment options, with RAI therapy being first-line treatment for most patients with toxic adenoma or toxic multinodular goiter. With both RAI and surgery being definitive treatments, the choice predominantly depends on patient factors and goiter characteristics. RAI is usually preferred in older patients with high surgical risk due to comorbidities and in patients with small- to moderate-sized adenomas without compressive symptoms. In contrast, surgery may be preferred in patients with large goiters, especially in cases of compressive symptoms and suspicion of thyroid cancer, or when there is a need for rapid control of hyperthyroidism. More recent but accumulating evidence indicates that prolonged administration of low-dosage ATDs can also be an effective therapeutic strategy, particularly in elderly patients or in those who are poor candidates for RAI or surgery.

Graves Disease

Although all 3 treatment modalities are generally effective in patients with Graves disease, ATDs are often favored by patients as an initial therapeutic approach.⁵ Notably, individuals with Graves disease treated with RAI have reported a lower quality of life up to 10 years after therapy compared with those managed with ATDs or thyroidectomy.

Carbimazole and its active metabolite, methimazole (MMI), are generally preferred over propylthiouracil (PTU), owing to their superior efficacy and more favorable safety profile. According to both American and European clinical guidelines, patients with newly diagnosed Graves hyperthyroidism are typically treated with carbimazole or MMI for a duration of 12 to 18 months.^{4,5} Treatment may be discontinued if serum TSH levels have normalized and TRAb are no longer detectable. In cases where TRAb remain elevated during therapy or relapse occurs following drug withdrawal, patients may opt for a second course of carbimazole/MMI—commonly for another 12 months or longer—or choose definitive treatment with RAI or thyroidectomy. While relapse rates following a single course of ATD therapy are relatively high (approaching 50%), a second treatment course can result in sustained remission in more than 75% of patients.¹⁰ Furthermore, recent studies suggest that long-term or even lifelong administration of low-dosage carbimazole/MMI is a safe and effective alternative strategy.⁶

Agranulocytosis is a rare but serious adverse effect of ATD therapy, occurring in fewer than 0.5% of treated patients and most frequently within the first 3 months of therapy. Patients should be explicitly instructed to seek immediate medical evaluation if they develop fever and/or a sore throat. If agranulocytosis is confirmed, ATDs must be permanently discontinued. ATD therapy may be administered using a dose-titration (monotherapy) approach aimed at maintaining euthyroidism, or by employing a “block-and-replace” regimen, in which higher ATD doses are used to completely inhibit thyroid hormone

production in combination with levothyroxine supplementation. Overtreatment with ATDs leading to hypothyroidism should be avoided, as this may precipitate or exacerbate thyroid eye disease in patients with Graves disease.

When RAI therapy is administered to patients with Graves disease, permanent hypothyroidism develops in approximately 50% to 85% and occurs more frequently with higher administered activities. The most clinically significant adverse effect of RAI therapy is the development or progression of thyroid eye disease, with cigarette smokers being at particularly increased risk. Consequently, RAI is contraindicated in patients with severe Graves orbitopathy. In patients with mild orbitopathy or in those at increased risk for de novo thyroid eye disease—including smokers, patients with severe or unstable hyperthyroidism, or those with high serum TRAb levels—prophylactic glucocorticoid therapy is recommended at the initiation of RAI treatment. Although multiple studies have demonstrated no overall increase in cancer incidence or mortality following RAI, some data suggest a potential dose-dependent association with increased mortality from solid malignancies¹¹; however, these findings remain controversial.

Thyroidectomy can also be considered as a first-line treatment option in selected cases, based on patient preference or in situations where ATDs or RAI are ineffective, poorly tolerated, or contraindicated, such as in patients with severe Graves orbitopathy.

Novel Treatment Options

Treatment modalities have remained similar for decades and have important limitations, such as the high relapse rates after withdrawal of ATDs and permanent hypothyroidism after RAI or surgery. In recent years, drugs with novel potential treatment targets for Graves disease have been tested in small and mainly open-label phase I and II clinical studies. Their mechanisms of action include: (1) restoration of immune tolerance (immunomodulatory TSH receptor peptides); (2) counteracting TSH-receptor

signaling (TRAb blockers, small molecular TSH receptor antagonists); (3) modulating B-cell function and activation (rituximab, iscalimab, belimumab); and (4) inhibiting IgG recycling by neonatal Fc receptor blockade (rozanolixizumab, efgartigimod). Large randomized multicenter trials are anticipated in the coming years to establish or refute these promising yet preliminary results.

Hyperthyroidism and Pregnancy (Planning)

Overt hyperthyroidism during pregnancy has been associated with a wide range of adverse maternal and neonatal outcomes, including an increased risk of miscarriage, intrauterine fetal demise, preeclampsia, preterm delivery, and low birth weight.¹² Available data indicate that these risks are substantially reduced or even absent in women who receive timely and adequate antenatal care and achieve appropriate biochemical control of hyperthyroidism.¹³

Treatment with antithyroid drugs during early gestation, particularly between gestational weeks 5 and 11, is associated with a small but clinically relevant risk of congenital malformations. Consequently, women with hyperthyroidism who are planning pregnancy are ideally treated with definitive therapy prior to conception. When ATDs are given during the first trimester of pregnancy, the type and severity of these teratogenic effects differ between agents, with overall patterns generally favoring PTU over carbimazole/MMI during this critical developmental window.

When radioactive iodine is selected as definitive treatment, women are typically advised to postpone pregnancy for a period of 6 to 12 months to minimize potential radiation-related risks. In addition, clinicians should be aware that serum TRAb may transiently rise following RAI therapy and can remain elevated for up to 1 year. Because TRAb are capable of crossing the placenta, persistently elevated levels during pregnancy may stimulate the fetal thyroid gland,

thereby increasing the risk of fetal or neonatal hyperthyroidism.

Clinical Case Vignettes

Case 1

A 30-year-old woman is referred by her general practitioner because of de novo Graves disease. She originally presented with weight loss, nervousness, and tachycardia. One week ago, she was prescribed a β -adrenergic blocker and MMI, 30 mg daily.

On physical examination, she has a diffuse goiter but no signs of orbitopathy.

Her family history is positive for Graves disease (her paternal grandmother and paternal aunt).

As part of the diagnostic workup, her general practitioner ordered thyroid function tests:

TSH = <0.001 mIU/L (0.4-4.3 mIU/L)

Free T_4 = 6.9 ng/dL (0.7-1.5 ng/dL) (SI: 89.0 pmol/L [9.0-19.0 pmol/L])

TRAb = 10.0 IU/L (<1.9 IU/L)

If she is treated with an ATD for 12 to 18 months, what is her risk of relapse?

- A. $<15\%$
- B. $15\%-45\%$
- C. $45\%-65\%$
- D. $>65\%$

Answer: D) $>65\%$

Several factors are associated with an increased risk of recurrence of Graves disease after an initial period of ATD therapy. These factors include male gender, age younger than 40 years, severe hyperthyroidism at presentation, moderate to severe orbitopathy, high TRAb levels at presentation, persistence of TRAb during ATD treatment, and cigarette smoking. A prospective observational study showed that based on a score with 4 clinical markers (age, free T_4 , TRAb, and goiter size) patients in the highest risk group have a 68% risk of recurrence after 1 year of treatment with ATDs (Answer D).¹⁴

Case 1, Continued

She does not currently desire pregnancy, but this will likely become a more realistic wish in the next 2 years.

Which of the following treatments would be best for her Graves disease?

- A. MMI monotherapy in lowest possible dosage
- B. PTU monotherapy in lowest possible dosage
- C. Block and replace therapy with MMI
- D. RAI therapy

Answer: D) RAI therapy

Although ATD therapy is the preferred initial therapy in most patients, there are good reasons to consider an immediate choice for definitive treatment in this patient. Based on her initial presentation, she will likely have a relapse after initial treatment with ATD for 12 to 18 months. This would mean that by the time her pregnancy wish becomes real, she will likely have a relapse of Graves disease. For that reason, I would discuss a definitive treatment at this stage because exposure to ATDs during the first trimester of pregnancy is associated with an increased risk of congenital malformations. Therefore, RAI therapy (Answer D) would be my preferred choice.

However, it should be noted that the only truly correct option is shared decision-making with the patient. All of the listed options have advantages and disadvantages; therefore, the best choice should be made together with the patient, weighing the pros and cons of the treatments for the health of a future pregnancy, with consideration for both fetal and general maternal health. If an ATD is selected, PTU (Answer B) is not a first-line treatment for patients who are not trying to conceive due to the risk of severe liver damage. PTU is generally considered a second-line treatment after MMI (Answers A and C).

Women who receive ^{131}I treatment for Graves disease should be advised to defer pregnancy for at least 6 months to minimize the potential adverse effects of RAI (as extrapolated from data on ^{131}I treatment for differentiated thyroid

cancer). Additionally, her serum TRAb and/or TSI concentrations will likely increase after RAI administration, but these generally return to pretreatment values 12 to 18 months after therapy.

Case 2

A 67-year-old woman is referred to the endocrinology clinic for evaluation of biochemical hyperthyroidism detected during routine cardiovascular follow-up. She reports mild symptoms over the past several months, including occasional palpitations, reduced exercise tolerance, and fatigue, without weight loss, tremor, or heat intolerance.

Her medical history reveals ischemic heart disease with prior coronary revascularization, chronic atrial fibrillation treated with anticoagulation, chronic obstructive pulmonary disease, and stage 3 chronic kidney disease. She lives alone and has limited social support.

On physical examination, she has an irregular pulse rate of 82 beats/min and a visibly enlarged, nodular thyroid gland. There are no clinical signs of thyroid eye disease.

Laboratory test results:

Serum TSH = 0.04 mIU/L (0.4-4.3 mIU/L)
 Free T₄ = 1.6 ng/dL (0.7-1.5 ng/dL) (SI: 21.0 pmol/L [9.0-19.0 pmol/L])
 Total T₃, normal
 TPO antibodies, negative
 TRAb, negative

Thyroid ultrasonography demonstrates a markedly enlarged multinodular thyroid with several nodules exceeding 4 cm. Thyroid scintigraphy reveals multiple autonomously functioning nodules with suppression of the surrounding thyroid tissue, consistent with toxic multinodular goiter.

Which of the following is the most appropriate management strategy for this patient?

- A. Total thyroidectomy
- B. RAI therapy
- C. Observation without treatment given mild symptoms
- D. Initiation of long-term, low-dosage ATD therapy
- E. Initiation of ATD therapy for 18 months, and then check if hyperthyroidism resolves

Answer: D) Initiation of long-term, low-dosage ATD therapy

Although RAI therapy (Answer B) and surgery (Answer A) are traditionally considered definitive treatments for toxic multinodular goiter, both options present significant challenges in this patient. Surgical intervention carries an unacceptably high perioperative risk due to this patient's advanced age and multiple cardiovascular and pulmonary comorbidities. RAI therapy, while technically feasible, is complicated by logistical issues related to radiation safety precautions and the patient's limited ability to comply with posttreatment isolation requirements.

Observation without treatment (Answer C) is not appropriate, as even mild hyperthyroidism in patients of this age is associated with increased risks of atrial fibrillation progression, cardiovascular morbidity, and bone loss. ATD therapy for a fixed period of 12 to 18 months (Answer E) is not likely to result in sustained euthyroidism, as toxic nodular goiter is not an autoimmune condition, and spontaneous remission does not occur.

In this clinical context, long-term, low-dosage ATD therapy (Answer D) represents a safe, effective, and pragmatic management strategy. Low-dosage MMI can maintain biochemical euthyroidism with a low incidence of adverse effects, particularly when used in stable low dosages in elderly patients. This approach minimizes treatment-related risks while effectively controlling thyroid hormone excess, making it the preferred option in this patient.

Case 3

A 28-year-old woman with Graves disease contacts the outpatient endocrinology clinic to report that she has discovered she is pregnant and is currently estimated to be 4 to 5 weeks' gestation. The pregnancy was unplanned; had she anticipated conception, she would have sought medical advice beforehand. She expresses happiness about the pregnancy but is concerned about the implications of her thyroid disease and ongoing treatment for fetal health. Specifically, she asks whether she should continue, modify, or discontinue her current antithyroid medication.

The patient was diagnosed with Graves disease 7 months earlier and has since been treated with MMI, 10 mg daily. Thyroid function tests have demonstrated biochemical stability: her most recent serum TSH concentration, measured 8 weeks prior to presentation, was 1.9 mIU/L, comparable to a value obtained 16 weeks earlier. Despite biochemical euthyroidism, TRAb remain elevated (the most recent value was 4.5 IU/L [reference range <1.9 IU/L]). Her next appointment is scheduled for 2 weeks from now.

At the time of the call, the patient reports mild nausea, which she attributes to early pregnancy. She has no symptoms suggestive of thyrotoxicosis and otherwise reports feeling well.

Which of the following is the best management approach for this patient?

- A. Measure TSH and free T₄ as soon as possible, and base the management on the results
- B. Stop MMI and switch to PTU, 50 mg twice daily
- C. Measure TSH, free T₄, and TRAb tested as soon as possible, and base the management on the results
- D. Stop MMI and assess thyroid function the same day
- E. Reassure her and explain that you will check everything at the next visit in 2 weeks

Answer: D) Stop MMI and assess thyroid function the same day

Exposure to ATDs during the first trimester of pregnancy, including both MMI and PTU, is associated with an increased risk of congenital malformations. Given the well-documented teratogenic risk during early gestation, clinical decision-making aimed at minimizing fetal risk is of greater importance than awaiting repeat thyroid function testing in this patient, particularly because her thyroid function has remained biochemically stable for approximately 4 months before conception. Obtaining new laboratory results (Answers A, C, and E) could lead to a delay that unnecessarily prolongs fetal exposure during the critical period of organogenesis.

Available evidence indicates that the absolute risk of congenital anomalies is higher with MMI exposure than with PTU. Moreover, the spectrum of malformations differs between the 2 agents. PTU exposure is more commonly associated with relatively mild abnormalities, such as defects involving the face and neck or the urinary tract, whereas MMI has been linked to a broader and more severe range of congenital anomalies affecting multiple organ systems. Consequently, when antithyroid drug therapy is required during the first trimester, PTU—if available—is generally preferred over MMI.

Importantly, discontinuation of ATD therapy should always be considered first in early pregnancy, particularly in patients with a low anticipated risk of relapse. In this case, the likelihood that continued ATD therapy would be needed during the first trimester appears low. First, the average time to relapse of Graves hyperthyroidism after ATD withdrawal is approximately 3 months. As a result, should a relapse occur, it is likely to happen after the most critical teratogenic window has already passed. Second, several clinical factors are associated with a reduced risk of relapse, all of which are present in this patient: treatment with a low dosage of ATDs (<10 mg daily), stable euthyroidism for more than 6 months prior to pregnancy (preferably with a serum TSH value >0.35 mIU/L), and TRAb levels below 3 times the upper normal limit.

Taken together, these considerations support immediate cessation of ATD therapy (Answer D)

rather than switching from MMI to PTU (Answer B). Measurement of thyroid function tests at this time is primarily intended to establish a new biochemical baseline, facilitating interpretation of subsequent thyroid function results following withdrawal of MMI.

Key Learning Points

- Although ATD therapy is the preferred initial therapy in most patients with Graves disease, an immediate choice for definitive treatment can be considered in patients with a high risk of relapse and a desire for pregnancy in the near future. In these patients, the risks and benefits of definitive therapy vs ATDS must be considered.
- Long-term, low-dosage MMI represents a safe, effective, and pragmatic management strategy in selected patients with toxic nodular goiter.
- MMI can also be considered in patients with Graves disease.
- In hyperthyroid patients with a positive pregnancy test, discontinuation of ATD therapy should always be considered as a first step in early pregnancy, particularly in patients with a low anticipated risk of relapse (treatment with low dosage ATDs [<10 mg daily], stable euthyroidism for >6 months prior to pregnancy [preferably with serum TSH >0.35 mIU/L], and TRAb levels <3 times the upper normal limit).
- Restoring immune tolerance, interfering with pathological TSH receptor signaling, regulating B-cell activation and function, and targeting IgG recycling pathways represent promising emerging therapeutic strategies for Graves disease and are likely to substantially reshape its management in the coming years.

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Redefining the Role of Radioactive Iodine in Differentiated Thyroid Carcinoma

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Describe how tumor genotype-phenotype characteristics influence iodine avidity in differentiated thyroid cancer (DTC) and may guide approaches to radioactive iodine (RAI) therapy.
- Differentiate the roles of remnant ablation, adjuvant therapy, and therapeutic ^{131}I in low-, intermediate-, and high-risk DTC, based on current evidence and guidelines.
- Evaluate emerging strategies, such as MAPK pathway inhibition, to promote RAI redifferentiation and improve responses to RAI therapy in advanced metastatic disease.

Significance of the Clinical Problem

Exploiting the expression of the sodium-iodide symporter (NIS) for diagnostic and therapeutic strategies in thyroid follicular-derived cancers led to ^{131}I as one of the earliest targeted therapies for DTC. In 1942, the dramatic reversal in a severely cachectic patient with thyrotoxicosis from metastatic (likely follicular) thyroid cancer after serial high-dose ^{131}I therapies propelled RAI into widespread use for the disease. Despite the lack of randomized clinical trial evidence for RAI

in DTC at the time, the rationale for targeting NIS therapeutically was sound, and data from retrospective clinical studies firmly established RAI in clinical practice and national guidelines. Nearly a century later, scientific progress from the bench and bedside has enabled a more tailored approach to RAI therapy. Strategies today are guided by a better understanding of the clinicopathologic outcomes of DTC and tumor-driven genotype-phenotype properties, both of which influence sensitivity to RAI uptake and response to ^{131}I therapy.

Practice Gaps

- ^{131}I therapy has been the standard for DTC, with limited individualized approaches based on tumor genotype-phenotype properties.
- ^{131}I therapy is paradoxically often recommended for high-risk disease, yet patients with the most advanced DTC often fail to respond to RAI therapy.
- Understanding tumor biology and genomics may enable more individualized approaches to ^{131}I therapy, leading to better responses.

Cases and Discussion

Case 1: Low-risk papillary thyroid cancer—is there a benefit of ^{131}I therapy, and what dose is recommended?

A patient presents for postoperative evaluation of papillary thyroid cancer (PTC). She underwent a near-total thyroidectomy without complications. AJCC 8th edition TNM staging of her PTC is pT2 (2.7 cm) N1a (1 of 6 lymph nodes positive, 0.4 cm, no extranodal extension). Her postoperative thyroglobulin concentration is 0.3 ng/mL (0.3 $\mu\text{g/L}$) with negative thyroglobulin antibodies, cM0, stage I disease. Her TSH concentration is 1.6 mIU/L while taking levothyroxine, 125 mcg daily.

What Is the Role of RAI Therapy in Low-Risk PTC?

Postoperatively, in low-risk thyroid cancers such as this, the role of ^{131}I therapy is primarily to ablate benign remnant thyroid tissue (and possibly residual microscopic disease) to enable sensitive thyroglobulin and sonographic surveillance. Historically, doses for ^{131}I remnant ablation were empirically derived, typically 30 to 100 mCi. Data from large, albeit retrospective, clinical studies demonstrated excellent overall and recurrence-free survival in patients with stage I PTC, with outcomes equivalent to those with and without postoperative RAI ablation. These clinical observations prompted strong questioning of the routine use of RAI therapy in this setting. Progress in this area emerged from 2 randomized controlled trials (HiLo and ESTIMABL) of RAI ablation in patients at low risk. Despite the lack of a “no RAI” control arm, these landmark studies demonstrated the feasibility of an evidence-based approach for RAI therapy in DTC and, for the first time, established guidance of 30 mCi for remnant ablation (rTSH or hypothyroid-driven) in low-risk disease.⁵ The strength of the data from these trials enabled the subsequent design and completion of a randomized, controlled, noninferiority trial comparing no RAI (0 mCi) with 30 mCi ^{131}I postoperatively in patients with low-risk

disease. This study definitively supported clinical observations by demonstrating no benefit of RAI remnant ablation in low-risk PTC, with a median follow-up of 3 years.

New guidelines and clinical practices have appropriately adopted a limited, selective approach to remnant ablation for low-risk disease. If postoperative remnant ablation is recommended, an evidence-based dose of 30 mCi is appropriate but of uncertain benefit. This much-needed shift has affected preoperative and operative approaches for low-risk PTCs. Lobectomy alone is now a reasonable alternative to total thyroidectomy. Notable patient benefits include reduced surgical risks, preservation of thyroid hormone secretion, fewer adverse effects of RAI therapy, and a reduced financial burden associated with this disease.

Genotype-Phenotype Tumor Characteristics Appear to Predict RAI Responsiveness

Advances in our understanding of DTC pathophysiology, based on genomic and clinicopathologic features, enabled a refined 2022 World Health Organization classification of thyroid follicular-derived malignancies into 4 distinct tumor subtypes, namely (a) classic PTC/PTC subtypes driven by *BRAF* and *BRAF*-like variants; (b) follicular thyroid cancer (FTC)/invasive encapsulated follicular variant of papillary thyroid cancer (IE-FV-PTC), driven by *RAS* variants; (c) oncocytic thyroid cancer (OTC), driven by mitochondrial alterations and nuclear loss of heterozygosity (LOH)/copy number alterations; and (d) poorly differentiated thyroid cancer (PDTC), defined by solid, trabecular growth with mitoses/necrosis and often harboring *RAS* variants. The presence of mitoses and necrosis further subclassifies high-grade PTC, FTC, and OTC. This phenotype-genotype schema aligns with distinct clinicopathologic patterns of behavior, including patterns of spread, responsiveness to TSH suppression, ability to secrete thyroglobulin, and sensitivity to RAI, enabling a more tailored management approach today than the one-size-fits-all historical approach for DTC.

High-Risk PTC

High-risk PTC is most often driven by oncogenic *BRAF* with high MAPK output and often lacks high thyroglobulin secretion. Recurrent disease is most often locoregional, with a small percentage developing distant disease. A comprehensive genomic evaluation of nearly 500 PTCs from the Thyroid Cancer Genome Atlas (TCGA) provides important insights into the spectrum of *BRAF*- vs *RAS*-driven thyroid cancer.⁷ While *RAS*-driven IE-FV-PTC/PTC has high thyroid differentiation scores and likely retains iodine avidity (at least in part), *BRAF*-driven PTC is more heterogeneous, with low thyroid differentiation scores, and behaves in a “*BRAF*-like” manner (less likely iodine-avid). Subsets of *BRAF*-driven PTCs with high thyroid differentiation scores are more “*RAS*-like” and may retain thyroglobulin and NIS expression. This and other comprehensive genomic studies of patients with advanced PTCs show that the acquisition of additional alterations, including *TERT*, *PI3K*, *TP53*, and/or *SWI-SNF* complexes, correlates with high risk and/or distant disease for which RAI therapy is often of very limited benefit.⁸

Widely Invasive FTC and IE-FV-PTC

Widely invasive FTC and IE-FV-PTC are biologically equivalent tumor types characterized by a capsule. The presence of a capsule and/or vascular invasion defines malignancy and recurrence risk. These tumors are most often driven by oncogenic *RAS*. In high-risk and/or advanced disease, they characteristically retain thyroid gene expression, respond to TSH suppression, and secrete high thyroglobulin levels.^{9,10} Unlike PTC, these tumor types spread distantly rather than locally, except for some IE-FV-PTCs. Importantly, *RAS*-driven FTC/IE-FV-PTC retains RAI uptake and responds to ¹³¹I therapy, at least initially. Minimally invasive FTC/IE-FV-PTC has a very low risk of distant disease and/or recurrence, suggesting a likely limited role for postoperative remnant or adjuvant RAI in the absence of distant disease and low thyroglobulin levels.

Oncocytic Thyroid Cancer

OTC, formerly known as Hurthle-cell thyroid cancer, was previously viewed merely as a subtype of FTC. Comprehensive genomic evaluations of OTC have identified unexpected mitochondrial gene alterations in the electron transport chain, nuclear copy-number alterations with LOH, and alterations in the mTOR-AKT pathway.¹¹ These distinct genomic alterations likely contribute to their inherent insensitivity to RAI, a phenomenon long observed in the clinic. Recently, a white paper consensus statement produced by members of the International Thyroid Oncology Group for the first time argues against the routine use of RAI therapy in OTC.¹² This pivot, supported by the 2025 American Thyroid Association guidelines suggesting an individualized approach for OTC,¹³ provides future, more tailored strategies for the disease, including questioning the need for total thyroidectomy and supporting a more traditional oncologic systemic chemotherapy targeted approach for metastatic disease.

Poorly Differentiated Thyroid Cancer

According to the Turin criteria, PDTC is defined as a tumor with solid and/or trabecular growth patterns, absence of papillary nuclear changes, and mitoses or necrosis.¹⁴ Although these tumors are commonly *RAS*-altered, like FTC/IE-FV-PTC, they are clinically distinct from the latter and secrete little, if any, thyroglobulin. They are most often FDG-avid and lack iodine uptake. While RAI remains a standard approach for high-risk and advanced PDTC, these tumors, like OTC, are most often resistant to iodine uptake, and oncologic chemotherapy targeted therapies are often needed.

In summary, the distinct genotype-phenotype characteristics of DTC indicate distinct biologic properties, and individually tailored approaches are needed, including adjuvant and/or therapeutic ¹³¹I therapy.

Case 2: Is there a benefit of adjuvant ¹³¹I therapy in high-risk disease?

- **Case 2a:** A patient presents status post total thyroidectomy. Final pathology reveals tall-cell PTC with gross extrathyroidal extension into the strap muscles. Ten positive central and lateral nodal metastases are found, confirming preoperative imaging findings (largest focus 2.5 cm), and there is no extranodal disease. The postoperative thyroglobulin concentration is 1.2 ng/mL (1.2 µg/L), with negative thyroglobulin antibodies.
- **Case 2b:** A postoperative patient presents after a lobectomy for a follicular neoplasm. The final pathology documents a 4.8-cm FTC with 6 foci of capsular invasion and at least 3 to 4 foci of angioinvasion. No lymph nodes were resected because preoperative ultrasonography showed no adenopathy. TNM tumor staging is pT3 N0 Mx.
- **Case 2c:** Same as above, but the patient has minimally invasive FTC.

Adjuvant RAI in High-Risk Disease

Adjuvant RAI is often recommended for high-risk DTC, defined pathologically by large tumors (>4 cm), gross extrathyroidal extension, more than 5 to 6 nodal metastases and/or large nodal disease, presence of and/or increased mitoses/necrosis, multifocal capsule and/or vascular invasion, and histologic progression (eg, tall-cell variant).¹³ Although RAI is the standard of care for high-risk and advanced disease, responses to RAI are often minimal and discordant across DTC subtypes. The best responses to RAI, particularly biochemically, are seen in *RAS*-driven FTC/IE-FV-PTC, which, however, are often the minority of cases in clinical trials. PTC and subtypes driven by *BRAF* and *BRAF*-like variants exhibit widely variable and/or mixed responses in lower-intermediate-risk tumors. High-grade PTC and/or FTC, defined by the presence of mitoses/necrosis and driven by *BRAF* or *RAS* alterations, as well as concurrent “high-risk” alterations (*TERT*, *SWI-SNF*, *PI3K*,

TP53), respond poorly to therapeutic and/or empiric ¹³¹I, owing to minimal iodine avidity. OTC and most PDTTC, with distinct genomic fingerprints, appear intrinsically refractory to ¹³¹I therapy. Thus, despite the routine use of RAI in the highest-risk disease, a striking paradox is that the more clinically and genomically advanced the disease, the less responsive it is to RAI.

In 2013, preclinical work from Jim Fagin’s lab at Memorial Sloan Kettering Cancer Center provided, for the first time, a targetable, genomic-driven mechanism of RAI-refractory disease.¹⁵ Using a murine model of *BRAF*-induced PTC, the investigators demonstrated that MAPK activation not only induced PTC but also globally inhibited thyroid gene expression, including *NIS*, thereby reducing iodine incorporation into thyroid cancer cells. Inhibiting *BRAF* upstream or *MEK* downstream restored iodine uptake in PTC, representing a pivotal moment in our understanding of the pathogenesis of DTC. This landmark translational study served as the basis for subsequent clinical trials and off-label MAPK-targeted approaches to iodine uptake and ¹³¹I therapy in both adjuvant and therapeutic settings for high-risk and/or advanced thyroid cancers.

The ASTRA phase 3, randomized, placebo-controlled trial was the first to assess the role of adjuvant RAI in high-risk disease by targeting MAPK to improve response to RAI. The field’s commonly held dogma was that adjuvant RAI could reduce recurrence by 50%, but no prior clinical trials had tested this. Retrospective studies challenged the benefit of RAI for intermediate-risk nodal disease. In ASTRA, patients were randomly assigned 2:1 to a MEK inhibitor (downstream of *BRAF*, *RAS*, and/or *RET* alterations) or placebo for 1 month, followed by 100 mCi of ¹³¹I postoperatively, with 18-month follow-up. The study endpoints were complete biochemical and structural response after RAI therapy. In both arms, complete response was strikingly low, with 60% of patients not achieving it. Although there was no “no RAI” control arm, the limited responsiveness of 100 mCi RAI in both arms, including in *BRAF*- and *RAS*-driven tumors,

challenges the long-perceived notion that adjuvant RAI therapy is beneficial in high-risk disease. Although complete response was the study's endpoint, it is unclear whether postoperative RAI may reduce reoperations or ethanol ablation for locally recurrent disease, which often plagues patients with PTC. Most importantly, although there were no differences in outcomes between *BRAF*- and *RAS*-driven tumors, the limited number of *RAS*-driven cases limits the ability to definitively assess the efficacy of RAI in this setting. High-risk, *RAS*-driven FTC and/or IE-FV-PTC, defined as widely invasive with more than 4 foci of capsular invasion and/or angioinvasion, uncommonly recur locally; rather, distant disease to the lungs and/or bone is the most common pattern of spread. The goal of adjuvant RAI in this context is to “ablate” microscopic residual disease, and thus it requires both thyroglobulin and structural imaging (often of the lungs) for accurate assessment of disease status on surveillance. Most DTC clinical trials are framed around the biology of PTC, for which local recurrences are most common, and neck ultrasonography is the primary tool for surveillance. The benefits of adjuvant RAI in *RAS*-driven FTC/IE-FV-PTC may be underestimated due to limited case numbers and incomplete tumor assessments.

In PTC, attempts to restore RAI avidity with MEK inhibition failed to reduce recurrences (most often locoregional), and the role of adjuvant RAI, although standard of care, remains paradoxical. An unanswered question from ASTRA is whether combination MAPK inhibition with dabrafenib plus trametinib for *BRAF*-mutant PTC may affect responses to adjuvant RAI therapy compared with MEK inhibition alone. Additionally, preclinical data suggest that targeting *BRAF*, as well as induced receptor tyrosine kinases, such as *HER2*, may improve RAI responsiveness in this tumor subtype. Importantly, expanded clinically meaningful endpoints, such as the number of reoperations or ethanol ablations, use of external-beam therapy, and time to systemic therapy for advanced, recurrent disease, may help clarify

the scope of RAI in high-risk disease beyond biochemical and structural endpoints.

In summary, adjuvant ^{131}I therapy may be particularly useful for *RAS*-driven FTC/IE-FV-PTC, where MEK inhibition may enhance responses and improve outcomes. The role of adjuvant RAI in *BRAF*-driven PTC remains unclear, but current data suggest it is largely ineffective. Subsets of PTC may respond better to ^{131}I therapy after MAPK inhibition, perhaps informed by biomarkers of RAI responsiveness (*see below*). In OTC, RAI provides limited to no benefit, and such tumor types are excluded from RAI redifferentiation studies. Future mechanistic studies may clarify whether altered metabolic pathways in this disease can be targeted to influence tumorigenesis and/or iodine avidity. Likewise, PDTC (Turin classification) is largely refractory to RAI, and alternative strategies for high-risk disease, such as external radiation, may be better tailored to high-risk local disease.

Case 3

Case 3a: A patient presents with pulmonary metastases (0.8 to 1.5 cm), too numerous to count, in the setting of PTC (T3 [5.3 cm], N1b [15 positive lymph nodes]). The postoperative thyroglobulin concentration is 2.5 ng/mL (2.5 µg/L). Genomic testing of tumor tissue is positive for the *BRAF* V600E variant and *TERT* alterations. The patient receives 150 mCi of RAI postoperatively, and a posttherapy scan shows no iodine uptake in the lungs. Six months later, the lung nodules are stable or minimally increased by 1 to 2 mm. The patient remains asymptomatic.

What is the benefit of RAI postoperatively in this case? Is there a role for additional ^{131}I therapy?

Case 3b: A patient with an 8-cm, widely invasive FTC presents with bilateral pulmonary metastases, up to 9 mm in diameter, and a thyroglobulin concentration of 145 ng/mL (145 µg/L) that has been slowly rising.

What is the approach for RAI in this context? If the patient has received ^{131}I therapy with a partial response, is there a role for additional RAI therapy?

Case 3c: A patient presents postoperatively with a 4.9-cm, widely invasive OTC. FDG PET-CT shows FDG-avid hilar adenopathy and pulmonary metastases (the largest focus measuring 1.2 cm).

What is the role of RAI for metastatic OTC?

^{131}I Therapy for Metastatic Disease

The presence of distant metastases, often in the lung and/or bone, defines advanced disease for which therapeutic high-dose ^{131}I is the standard of care.

In distantly metastatic PTC and/or FTC (including IE-FV-PTC), responses to high-dose ^{131}I therapy are rarely curative; exceptions include young patients and select older patients with *RAS*-altered, micronodular pulmonary metastases that express high thyroglobulin levels or have high levels of thyroid differentiation.¹⁷ OTC and PDTC, as detailed earlier, are well documented to be inherently refractory to iodine uptake and ^{131}I therapy, with rare exceptions.

The selumetinib-induced RAI redifferentiation pilot clinical trial, published in the *New England Journal of Medicine* and led by Dr. Alan Ho at Memorial Sloan Kettering Cancer Center, was the first human proof-of-principle study demonstrating improved responses to ^{131}I therapy after MAPK pathway inhibition.¹⁸ This pilot study of 20 patients with metastatic disease refractory to prior ^{131}I therapies demonstrated restoration of iodine uptake in 12 of 20 patients, with increased SUV in most disease foci, as measured by ^{124}I PET. Treatment with high-dose ^{131}I in 12 patients with sufficiently restored iodine uptake resulted in partial Response Evaluation Criteria in Solid Tumors (RECIST) responses and/or stable disease and significant reductions in thyroglobulin. Interestingly, only 1 of 9 patients with *BRAF*-variant tumors had restoration of iodine uptake, whereas all 5 *RAS*-driven tumors redifferentiated, consistent with clinical observations but discordant with preclinical data.

A completed phase 2 randomized controlled study of selumetinib vs placebo (2:1 randomization) for 1 month, followed by 150 mCi of RAI for iodine-avid disease, will further clarify the benefits of RAI redifferentiation in advanced disease. Data from this study may inform approaches to initial RAI therapy in advanced disease, particularly for *RAS*-driven FTC/IE-FV-PTC, if sufficiently powered.

At Mayo Clinic Rochester, we published a comprehensive retrospective study of off-label RAI redifferentiation in patients with advanced PTC, FTC, and PDTC referred to medical oncology for advanced disease. All patients (with or without redifferentiation and ^{131}I treatment) were followed for 2 years, with comprehensive clinical, biochemical, genomic, and structural outcomes collected. *BRAF*-mutant PTC/HG-PTC was treated with a combination of dabrafenib plus trametinib for 1 month, followed by a low-iodine diet and a thyrotropin alfa-stimulated ^{123}I whole-body scan. Patients with positive scans underwent a modified dosimetry-guided high-dose ^{131}I therapy (median dose 250 mCi). For *RAS*-mutant disease, trametinib monotherapy was used. Patients with negative RAI scans were not treated with ^{131}I therapy but continued surveillance follow-up.

As intimated in a prior pilot study, all *RAS*-driven tumors, primarily FTC/IE-FV-PTC with high thyroglobulin levels, redifferentiated and responded structurally and biochemically to high-dose ^{131}I therapy. Notably, other studies have since shown that *RAS*-driven tumors also respond to empiric ^{131}I therapy after MEK inhibition despite negative pretherapy scans, emphasizing the significance of RAI redifferentiation in these tumors. In our retrospective study, there was no “control arm” for *RAS*-driven FTC/IE-FV-PTC, as all subtypes redifferentiated and received ^{131}I therapy, which may have underestimated the effect of ^{131}I therapy on this tumor type when assessed by endpoints such as progression-free survival, overall survival, and time to systemic therapy.

Only about 30% of *BRAF*-driven PTC/PDTC redifferentiated despite combination *BRAF*-MEK inhibition, and responses to ^{131}I therapy were

mixed and often disappointing. There was no difference in time to systemic therapy between those that did redifferentiate and received ^{131}I therapy and those that did not redifferentiate and did not receive ^{131}I .

Overall survival in this cohort was paradoxically lower in the RAI redifferentiated group than in the nonredifferentiated group. Two patients in the RAI redifferentiated group developed anaplastic disease transformation and died. One anaplastic thyroid cancer arose in a patient with a *RAS*-driven FTC who initially had the most striking and best response to RAI therapy. Genomic analysis of her anaplastic thyroid cancer revealed multiple alterations across the spectrum of advanced disease, raising important questions about the effect of ^{131}I therapy on genomic instability and/or the selection and progression of non-iodine-avid clonal tumor populations after RAI therapy, with or without RAI redifferentiation.

In summary, published data on RAI redifferentiation indicate that sensitivity is highest in *RAS*-driven follicular phenotypes compared with *BRAF* (or *RET*) papillary phenotypes, including among patients with negative diagnostic whole-body scans. Short-term follow-up and/or a lack of matched genotype-phenotype controls may minimize benefits in tumor subtypes, particularly in *RAS*-driven tumors. RECIST criteria, the gold standard for oncologic clinical trials, are often inappropriate eligibility criteria for RAI therapy trials, as the physics of ^{131}I predicts better responses in micronodular than macronodular disease. Techniques in RAI therapy and RAI redifferentiation likely affect outcomes. Responses to RAI therapy are influenced by the type and duration of RAI redifferentiation drug therapies, dosimetry vs empiric dosing of ^{131}I , use of diagnostic ^{131}I vs ^{124}I PET for identification and quantification of iodine uptake and estimated radiation delivery to foci of disease, and the presence of other molecular alterations (eg, in the SWI-SNF complex).²⁰ Incorporating such parameters into clinical trial designs often becomes unwieldy, requiring large numbers of

patients, significant time, and substantial cost. Off-label approaches to RAI redifferentiation offer flexibility and real-time adaptation but are highly heterogeneous and lack control arms, making data difficult to compare across practices.

Our practice has evolved so that RAI therapy for patients with metastatic disease can now be tailored by genotype-phenotype and informed by both translational and clinical data, including randomized, nonrandomized, and retrospective datasets. Despite their challenges and limitations, these approaches remain superior to historical one-size-fits-all approaches grounded in rational, albeit theoretical, principles that are heavily ingrained in clinical guidelines. For high-risk and/or metastatic *RAS*-driven FTC/IE-FV-PTC with high thyroglobulin levels, with or without RAI avidity on diagnostic iodine whole-body scan, responses to high-dose ^{131}I therapy are likely to improve substantially after inhibition of the MAPK pathway. In *BRAF*-driven PTC, combination MAPK inhibition in select cases may also improve outcomes after ^{131}I therapy, but there is a clear need to improve iodine incorporation into these tumor foci. Expanded clinical endpoints, such as the number of surgeries, ablations, and/or time to systemic therapies, are important and may expand the benefits of RAI therapy. They should be considered in data analyses. Biomarkers of response to RAI redifferentiation in *BRAF*-driven PTC, such as the thyroid differentiation score, may identify “exceptional” responders for whom MAPK inhibition may improve partial or complete response to ^{131}I therapy. Biomarkers of nonresponders to RAI redifferentiation/RAI avidity may better inform non-iodine-based therapeutic approaches.

The refinement of our approaches for DTC reflects the art of medicine, in which preclinical and clinical evidence, despite limitations and gaps, is incorporated to rationally inform current clinical practices and future clinical trials, thereby incrementally improving approaches for patients with DTC.

Key Learning Points

- DTC genotype-phenotype characteristics inform iodine uptake sensitivity and responsiveness to ^{131}I therapy.
- In low-risk DTCs, there is no clear benefit from postoperative ^{131}I therapy, enabling more tailored approaches, including the type of surgery that can be performed.
- Targeting the MAPK pathway in patients with metastatic DTC may enhance iodine avidity and tumor responses to ^{131}I therapy.

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Targeted Therapy in Advanced Thyroid Cancer

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Recognize the role of driver molecular alterations in advanced differentiated thyroid cancers (DTCs) and the need to identify them to make optimal treatment recommendations for patients who require systemic therapy.
- Explain how the genotype-phenotype correlation in DTC, which links molecular alterations to histologic subtypes, provides insights into the varied natural histories of disease and offers opportunities to optimize systemic therapy for patients with advanced disease.

Significance of the Clinical Problem

Most deaths due specifically to thyroid cancer occur in patients with radioiodine (RAI)-refractory DTC. A decade ago, treatment options for patients with advanced RAI-refractory DTC were limited to vascular endothelial growth factor receptor–targeting multikinase inhibitors (MKIs). MKIs have demonstrated clinical efficacy in tumor shrinkage, progression-free survival, and, in some cases, overall survival benefits, but their treatment-related adverse events can be impactful. Driver molecular alterations, including *BRAF* and *RAS* variants and *RET/NTRK/ALK* and *ROS1* gene rearrangements, are often targetable with gene-specific systemic therapy. Decision-making regarding the best approach to systemic therapy in patients with

advanced RAI-refractory DTC, such as selecting the best first-line therapy and the optimal sequence of treatments, is nonetheless challenging.

Practice Gaps

- Molecular diagnostic testing of tumor tissue is indicated for every patient with advanced RAI-refractory DTC who needs systemic therapy and should be performed whenever possible before starting first-line therapy. However, many patients still do not undergo this testing despite its widespread availability.
- There is significant interest in leveraging molecular driver alterations affecting the MAPK pathway to facilitate RAI treatment for RAI-refractory disease, yet gold-standard randomized phase III data are lacking.
- Highly effective gene-specific therapy targeting *N/H/K RAS* alterations, which are common in DTCs, is not yet available. A new generation of *RAS*-specific inhibitors is in clinical development, and studies focused on *RAS*-driven thyroid cancer are urgently needed.

Clinical Case Vignettes and Discussion

Case 1

In most patients with advanced, RAI-refractory DTC, the disease is limited to the locoregional area at the time of initial diagnosis. This was the case with Patient 1, a 60-year-old man who presented with a left neck mass in 2014. Ultrasonography revealed a 1.7-cm suspicious left

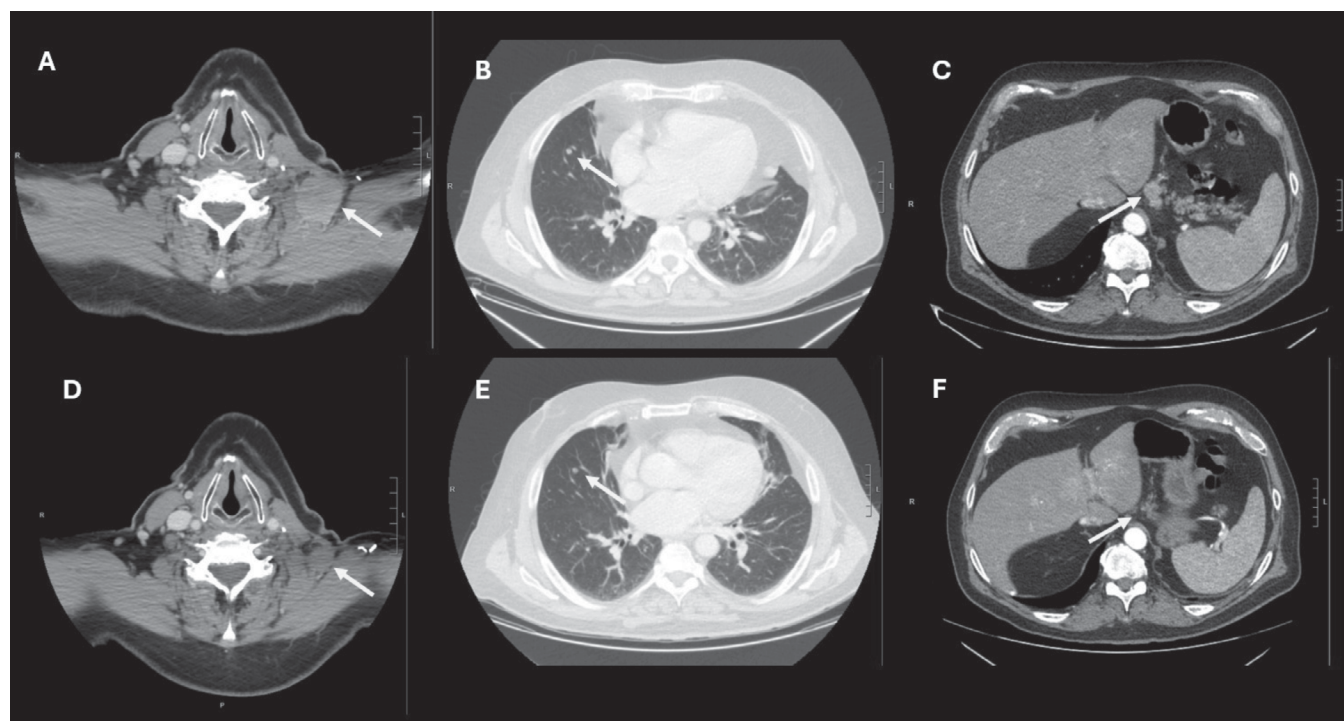
thyroid nodule and multiple enlarged left lateral neck nodes measuring up to 2.1 cm. Neck CT revealed a 1.7-cm left thyroid nodule and multiple suspicious lymph nodes in left levels II through IV. Fine-needle aspiration (FNA) showed papillary thyroid carcinoma (PTC). He underwent total thyroidectomy with bilateral central and left lateral neck dissection. Pathology showed PTC, tall cell variant, with minimal extrathyroidal extension, lymphovascular invasion, and perineural invasion. In the central neck, 4 of 15 nodes were involved, and 7 of 31 lateral nodes were involved, the largest of which was 4.6 cm, with extranodal extension. Immunohistochemistry (IHC) for the *BRAF* V600E variant was positive. The patient then enrolled in the ASTRA trial, which investigated the MEK inhibitor selumetinib vs placebo as pretreatment for adjuvant RAI in patients with DTC at high risk for primary treatment failure.¹ He received 100 mCi RAI under thyrotropin alfa stimulation. Whole-body imaging 5 days later showed uptake

in the bilateral thyroid bed and in the left lateral neck.

TSH was kept suppressed. Serum thyroglobulin (Tg) remained less than 1 ng/mL (<1 µg/L). The patient developed recurrent disease in the left neck 2 years after thyroidectomy and underwent revision neck surgery. Nine months later, he had FNA-confirmed recurrent disease in the left neck. Diagnostic RAI whole-body imaging showed no uptake. A second left revision neck surgery was performed. Pathology showed multiple deposits of tall-cell-variant PTC infiltrating fibroadipose and connective tissues, with no definite lymph node tissue present. Next-generation sequencing from the second revision neck specimen confirmed the presence of the *BRAF* V600E variant, plus *TERT* promoter C228T and *CIC* E1366K comutations.

By May 2019, the patient developed locoregionally recurrent and distant metastatic disease with left cervical adenopathy up to 3.4 cm, scattered small lung nodules up to

Figure 1. Case 1 Patient CT



Arrows indicate the following findings: Panel A, left cervical adenopathy in May 2019; Panel B, lung metastasis in May 2019; Panel C, gastrohepatic adenopathy in May 2019; Panel D, left cervical adenopathy in July 2019; Panel E, lung metastasis in July 2019; Panel F, gastrohepatic adenopathy in July 2019.

[Color—Print (Color Gallery page CG21) or web & ePub editions]

1.4 cm, and a 3.0-cm gastrohepatic nodal conglomerate. The suppressed Tg concentration was 4.6 ng/mL (4.6 μ g/L). He started systemic therapy with lenvatinib. The patient developed treatment-related hypertension that required antihypertensive therapy and, eventually, dosage reduction. After the first 2 cycles, he experienced a partial response (PR) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, with a 61% decrease in tumor measurements (*Figure 1, preceding page*). The Tg concentration decreased to 2.7 ng/mL (2.7 μ g/L). The patient required a second dosage reduction of lenvatinib due to treatment-related diarrhea. He remained responsive to lenvatinib for 48 months until oligoprogressive disease developed involving a thoracic vertebral body metastasis. Lenvatinib was held during stereotactic body radiotherapy and then resumed. Seven months later, in December 2023, lenvatinib was discontinued due to further disease progression involving the emergence of a mass in the left styloid parapharyngeal space.

In January 2024, second-line treatment with dabrafenib plus trametinib was initiated. By cycle 4, the patient's RECIST v1.1 tumor measurements met the criteria for PR, with a 31% decrease (*Figure 2*). During that time, Tg increased from 14

to 19 ng/mL (14 to 19 μ g/L). While on dabrafenib plus trametinib, the patient received a second 100 mCi dose of thyrotropin alfa-stimulated RAI. The stimulated Tg concentration was 120 ng/mL (120 μ g/L). On the subsequent whole-body scan, a solitary focus of uptake was seen in the left neck. Two months later, suppressed Tg dropped to 6.1 ng/mL (6.1 μ g/L). The patient required a dosage reduction due to treatment-related pyrexia syndrome, but otherwise dabrafenib plus trametinib was well-tolerated. He remained responsive for 22 months until multifocal thoracic spine metastases developed in November 2025. Dabrafenib plus trametinib was discontinued, and stereotactic body radiotherapy was administered to these lesions. Further systemic therapy, including cabozantinib or participation in clinical trials, is now under consideration.

Case 1 Discussion

This case depicts a common story of advanced RAI-refractory DTC. PTC is the most common histologic subtype of DTC, and the *BRAF* V600E variant is the most common driver alteration in PTCs. Most patients diagnosed with *BRAF* V600E-positive PTC do well over time, but when

Figure 2. Case 1 Patient CT and Post-RAI Whole-Body Scan



Panel A, left styloid parapharyngeal mass (arrow) in December 2023; Panel B, left styloid parapharyngeal mass (arrow) in April 2024; Panel C, Post-RAI whole-body scan in July 2024.

[Color—Print (Color Gallery page CG21) or web & ePub editions]

comutations are present, most often involving the *TERT* promoter, patients are more likely to experience recurrent RAI-refractory disease, and have a higher risk of thyroid cancer-specific mortality.² The well-known clinical benefit of combined BRAF- plus MEK-targeted therapy in patients with *BRAF* V600E-positive melanoma, as well as preclinical data demonstrating the efficacy of MAPK pathway inhibition in *BRAF* V600E PTC models, led to a multicenter randomized phase II study examining dabrafenib with or without trametinib in patients with progressive *BRAF* variant-positive RAI-refractory DTC.³⁻⁶ Fifty-three patients were enrolled. Patients were allowed to have received prior MKI treatment, although most were treatment naïve. The objective response rate by RECIST 1.1 and the median progression-free survival with dabrafenib monotherapy were 35% and 10.7 months, respectively; with dabrafenib plus trametinib, they were 30% and 15.1 months, respectively. Compared with the efficacy of lenvatinib in first-line treatment of progressive RAI-refractory DTC, regardless of DTC genotype, the evidence for the efficacy of dabrafenib with or without trametinib did not provide a convincing argument for replacing lenvatinib as the standard first-line treatment for patients with progressive *BRAF* variant-positive, RAI-refractory PTC.⁷⁻⁹ However, after the tissue-agnostic US FDA approval of dabrafenib plus trametinib for patients with unresectable or metastatic solid tumors harboring the *BRAF* V600E variant whose disease progresses after treatment, this regimen became available in 2023, and second-line dabrafenib plus trametinib was widely adopted for *BRAF* V600E-positive PTC following progression on lenvatinib or other MKIs. We now have even stronger data supporting the use of second-line dabrafenib plus trametinib in patients with *BRAF* V600E-positive, RAI-refractory PTC. In late 2025, results were presented from an international phase III trial comparing dabrafenib plus trametinib with placebo in patients with *BRAF* V600E-positive, RAI-refractory PTC who had received 1 or 2 prior MKIs.¹⁰ Median progression-free survival

was significantly longer with dabrafenib plus trametinib than with placebo: 12.8 months (95% CI, 10.2-21.2) vs 3.7 months (95% CI, 2.3-7.5), respectively. The objective response rate with dabrafenib plus trametinib was 57.4%. These better-than-anticipated results are expected to solidify the role of dabrafenib plus trametinib in treating patients with advanced *BRAF* V600E-positive, RAI-refractory PTC.

This case also highlights interest in redifferentiation for patients with advanced RAI-refractory DTC. PTCs driven by the *BRAF* V600E variant exhibit high MAPK pathway signaling, resulting in downregulation of thyroid differentiation genes, including those encoding the sodium-iodide symporter and TPO. This provides a rationale for blocking MAPK activation in *BRAF* V600E-positive PTC to facilitate RAI uptake in patients with RAI-refractory disease.¹¹ Although no phase III study has examined the clinical benefit of dabrafenib plus trametinib compared vs placebo before RAI treatment in patients with *BRAF* V600E-positive, RAI-refractory disease, MERAIODE was a multicenter, phase II, single-arm trial investigating this approach.¹² Twenty-four patients were enrolled. The primary outcome was the RECIST v1.1 response rate at 6 months, observed in 38% of patients, suggesting potential clinical benefit for some patients with this approach.

Case 2

A 16-year-old boy developed aplastic anemia. He was treated with high-dose chemotherapy and total-body irradiation, followed by a matched, unrelated bone marrow transplant. He has remained in remission since. At age 23 years, he presented with a persistent dry cough, dyspnea on exertion, dysphagia, and a right neck mass. Neck MRI showed a diffusely enlarged thyroid gland, circumferential encasement of the trachea with loss of fat planes between the tumor and the trachea, severe tracheal narrowing, and bilateral multistation cervical adenopathy, the largest of which was a 3.6-cm node in right level 2. Core-needle biopsy of a right neck node showed PTC

with columnar and focal hobnail features. *BRAF* V600E IHC was negative. PET-CT showed FDG-avid bilateral cervical and mediastinal adenopathy, diffuse FDG uptake in a multinodular thyroid gland, and no FDG uptake in a 3-mm lung nodule. Next-generation sequencing revealed a *CCDC6-RET* fusion. The case was reviewed by the multidisciplinary tumor board, which determined that the tumor was unresectable.

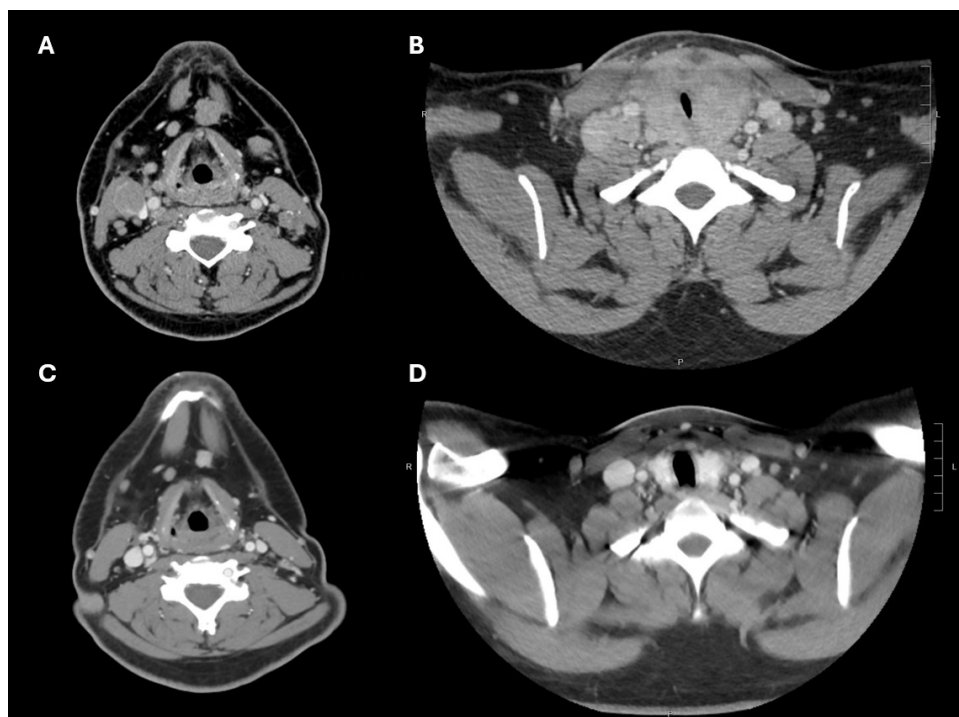
Systemic therapy was initiated with selpercatinib to achieve overall clinical benefit and, if a response was achieved, to make the disease resectable. Selpercatinib was dose-reduced due to QTc prolongation, which subsequently resolved. The patient's cough, dyspnea, and dysphagia resolved. After 2 cycles, tumor measurements decreased by 27% by RECIST v1.1. After 4 cycles of selpercatinib, tumor measurements decreased by 50%. After 8 months of treatment, the patient reported erectile dysfunction, a known selpercatinib treatment-related adverse event. He was treated with tadalafil. Selpercatinib was otherwise well tolerated. Restaging neck CT

showed significant improvement in bilateral thyroid gland enlargement, with circumferential tracheal involvement no longer present, and further improvement in bilateral neck adenopathy. Overall, there was a 61% decrease in tumor measurements (*Figure 3*). Planning for staged hemithyroidectomies with bilateral central and lateral neck compartment dissection is now underway. Postoperative RAI will be planned based on surgical outcomes, with consideration of pre-RAI selpercatinib treatment for redifferentiation vs RAI treatment alone.

Case 2 Discussion

A rich genotype-phenotype correlation is observed across the spectrum of DTC. Driver alterations, primarily pathogenic point variants, gene rearrangements, or fusions, are mutually exclusive. The *BRAF* V600E variant primarily gives rise to classic variant PTC, as well as tall cell and hobnail variants, whereas *RAS* (*N/H/K*) pathogenic variants most frequently give rise to

Figure 3. Case 2 Patient CT



Panel A, bilateral cervical adenopathy in June 2025; Panel B, circumferential tumor and tracheal narrowing in June 2025; Panel C, improved bilateral cervical adenopathy in February 2026; Panel D, improved circumferential tumor and tracheal narrowing in February 2026.

follicular thyroid cancer and follicular variant PTCs.¹³ Although oncogenic kinase fusions are less common than the *BRAF* V600E variant in PTC, PTC harbors the highest frequency of oncogenic kinase fusions across all solid cancers in adults.^{11,14} Fusions involving *RET* kinase are most common, followed by fusions involving *BRAF*, *NTRK 1* or *3*, *ALK*, and *ROS1*, in decreasing order of frequency. Oncogenic kinase fusions, seen more frequently in pediatric and young adult patients with DTCs and in thyroid cancers arising in patients previously exposed to ionizing radiation, give rise to characteristic histologic features, including multinodular growth, prominent intratumoral fibrosis, lymphovascular invasion, extrathyroidal extension, and lymph node involvement.¹⁵ In addition to harboring more aggressive clinicopathological features, kinase fusion–driven DTCs have worse clinical outcomes, particularly in older adults.^{16,17}

Although patients with advanced kinase fusion–positive DTC have been enrolled in clinical trials investigating MKIs, such as the DECISION and SELECT trials, which evaluated sorafenib and lenvatinib, respectively, outcome analyses for these patients are not available. However, clinical trials investigating *NTRK*- and *RET*-targeting small-molecule inhibitors have included a significant number of patients with advanced *NTRK*- and *RET* fusion–positive DTC.

NTRK 1, *2*, and *3* encode tropomyosin receptor kinase (TRK) neurotrophin proteins TRK A, B, and C, respectively.¹⁸ TRK proteins, which signal through the RAS/MAPK, PI3K, and PLC γ pathways, are normally expressed in neuronal tissues and play essential roles in nervous system embryogenesis and in the normal maintenance of the nervous system, including survival, cell proliferation, synaptic formation, and plasticity. Oncogenic kinase fusions involving *NTRK 1* and *3*, more often than *NTRK 2*, result from interchromosomal or intrachromosomal gene rearrangements that fuse the 3' region of the *NTRK* gene, encoding the kinase domain, with the 5' end of a partner gene that typically harbors transcription and homodimerization domains. The

resulting aberrant protein leads to constitutive oncogenic signaling. Oncogenic *NTRK* fusions are observed at very low frequencies in many solid tumors, and they drive a majority of several rare cancers, namely pediatric infantile sarcoma and salivary gland secretory carcinoma, and occur in approximately 5% and 25% of DTCs in adults and children, respectively. Across 3 phase I/II trials investigating the TRK-specific inhibitor larotrectinib in patients with any *NTRK* fusion–positive solid tumors, 29 patients with thyroid cancer (22 with DTC and 7 with anaplastic thyroid cancer [ATC]), were enrolled.¹⁹ As expected for a highly specific TRK kinase inhibitor with minimal off-target kinase inhibition, on-target adverse events included myalgia, fatigue, and dizziness and were primarily grade 1 or 2. Less common adverse events included elevated liver transaminases, anemia, and decreased lymphocyte count. Only 7% of patients required dose reduction, and no patient required treatment discontinuation due to adverse events. Among the 22 patients with DTC, the objective response rate by RECIST v1.1 was 86%. Responses were long-lasting, with progression-free survival rates of 100% and 84% at 1 and 2 years, respectively. In the 7 patients with anaplastic thyroid cancer, efficacy was disappointing. Although the objective response rate was 29%, median progression-free survival was only 2.2 months, and median overall survival was 8.8 months. Based on pooled phase I/II data, larotrectinib received the US FDA's first approval of a tumor-agnostic small-molecule inhibitor in 2018.

Entrectinib and repotrectinib have also been developed as TRK inhibitors. Entrectinib inhibits TRK A, B, and C, ROS1, and ALK kinases. In an integrated analysis of 121 adult patients with *NTRK* fusion–positive solid tumors enrolled in 3 phase I/II trials of entrectinib, which included 13 patients with thyroid cancer, the objective response rate was 54%, and the median progression-free survival and overall survival were both 19.9 months.²⁰ More recently, repotrectinib was developed as a next-generation inhibitor of TRK A, B, and C and ROS1 designed to improve durability of response and overcome acquired

solvent front resistance variants that emerge in patients previously treated with a TRK inhibitor.²¹ Of 120 evaluable *NTRK* fusion–positive patients, 6 were kinase inhibitor–naïve and 7 were previously treated with a TRK inhibitor for thyroid cancer. In the overall kinase inhibitor–naïve patient population, the objective response rate was 59% with a median progression-free survival of 30.3 months. In the previously treated population, the objective response rate was 48% with a median progression-free survival of 7.4 months. Although no head-to-head comparisons among larotrectinib, entrectinib, repotrectinib, and MKIs have been conducted, the available safety and efficacy data appear to favor larotrectinib as the optimal first-line therapy for patients with advanced *NTRK* fusion–positive DTC.⁹

The *RE*arranged in Transfection kinase gene (*RET*) is the most common oncogenic kinase fusion in DTC, occurring in approximately 10%, 30%, and 35% of PTCs in adults, children, and radiation-related cases, respectively.^{22–24} As with *NTRK* fusions, *RET* fusions cause constitutive activation of kinase signaling via the RAS/MAPK, PI3K, PLC γ , and other pathways. Selpercatinib and pralsetinib were similarly designed to potently and specifically inhibit RET, with minimal off-target kinase inhibition. The phase I/II trial LIBRETTO-001 enrolled 24 patients with MKI-naïve advanced *RET* fusion–positive DTC, and 41 previously treated patients, 4 of whom had anaplastic thyroid cancer.^{25,26} The most common adverse events, which were primarily grade 1 or 2, included hypertension, elevated liver transaminases, diarrhea, and fatigue. Thirty percent of patients had dose reductions, while only 2% discontinued selpercatinib because of treatment-related adverse events. In the treatment-naïve *RET* fusion–positive cohort, the objective response rate was 96%, with progression-free survival rates of 95% and 66% at 2 and 4 years, respectively. In previously treated patients, the objective response rate was 85%, and the median progression-free survival was 27.4 months. The results of LIBRETTO-001 led to the first US FDA

approval of a RET-specific inhibitor for *RET*-altered cancers in 2020.

Pralsetinib was studied in the phase I/II ARROW trial, which enrolled 25 patients with *RET* fusion–positive thyroid cancer, most of whom had received at least 1 prior MKI.²⁷ The safety profile of pralsetinib is similar to that of selpercatinib, apart from slightly more bone marrow suppression. The objective response rate was 91%, and the median progression-free survival was 25.4 months. Pralsetinib also received FDA approval for *RET* fusion–positive cancers in 2020. Again, no head-to-head comparison between a RET-specific inhibitor and an MKI in advanced *RET* fusion–positive DTC has been conducted. Based on the strength of the available safety and efficacy data, RET-specific inhibition is preferred over MKIs for first-line treatment of patients with advanced *RET* fusion–positive DTC.⁹

Finally, as in *BRAF* V600E–positive PTCs, early evidence of redifferentiation in *NTRK*- and *RET* fusion–positive disease treated with TRK and RET inhibitors is encouraging and is thought to likely offer clinical benefit in select cases.²⁸

Questions

How is the frequency of advanced RAI-refractory DTCs harboring actionable driver genomic alterations that may affect the choice of systemic therapy best described?

- A. Rarely present
- B. Uncommon, and may be relevant in first-line therapy
- C. Uncommon, but only relevant in second-line therapy
- D. Common, and may be relevant in first-line therapy
- E. Common, but only relevant in second-line therapy

Answer: D) Common, and may be relevant in first-line therapy

For a patient with progressive, *BRAF* V600E–positive, RAI-refractory PTC, what is the best sequence of systemic therapy based on currently available clinical trial data?

- A. Lenvatinib → cabozantinib → dabrafenib + trametinib
- B. Lenvatinib → dabrafenib + trametinib → cabozantinib
- C. Dabrafenib + trametinib → lenvatinib → cabozantinib
- D. Dabrafenib + trametinib → cabozantinib → lenvatinib
- E. Dabrafenib + trametinib + RAI (redifferentiation) → lenvatinib → cabozantinib

Answer: B) Lenvatinib → dabrafenib + trametinib → cabozantinib

Which of the following descriptions is most accurate for kinase fusion–driven DTC?

- A. More likely to occur in younger patients and may be effectively treated with gene-specific therapy
- B. More likely to occur in older patients and may be effectively treated with gene-specific therapy
- C. More likely to occur in younger patients and is unresponsive to MKI therapy
- D. More likely to occur in older patients and is unresponsive to MKI therapy
- E. More likely to occur in older patients and is rarely responsive to gene-specific therapy

Answer: A) More likely to occur in younger patients and may be effectively treated with gene-specific therapy

Conclusions and Future Directions

Driver molecular alterations are common in advanced RAI-refractory DTCs, and many are now targetable with highly effective, well-tolerated therapies. First- and second-line targeted therapy options are available. Thus, tumor next-generation sequencing, particularly with a platform that incorporates a robust method for

detecting oncogenic kinase fusions, is critical for every patient with advanced RAI-refractory DTC before initiating systemic therapy; we do not want to miss a single patient harboring a targetable alteration, given the availability of highly effective treatments.

Future studies are still needed. A definitive randomized controlled trial of redifferentiation, particularly in *BRAF* V600E–positive RAI-refractory PTC, remains a major unmet need in the field. Pan-RAS-specific targeted therapies are not yet established as standard treatment options in oncology, but several promising agents are in the pipeline. Lastly, new approaches are needed for patients receiving targeted therapy once acquired resistance develops.

Key Learning Points

- Every patient with advanced RAI-refractory DTC who needs systemic therapy should undergo tumor molecular testing to identify potentially targetable driver gene alterations before initiating systemic therapy. Potentially targetable driver gene alterations that will affect treatment decisions are common.
- Lenvatinib is considered the optimal first-line treatment for patients with progressive, *BRAF* V600E–positive, RAI-refractory PTC. Dabrafenib plus trametinib should be given to patients who experience progression on lenvatinib or are intolerant to it.
- For patients with *RET*- or *NTRK* fusion–positive RAI-refractory DTC, *RET*- or *TRK*-specific gene therapy should be the first-line treatment.

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TUMOR BIOLOGY

Management of Duodeno-pancreatic Neuroendocrine Tumors in Patients With Multiple Endocrine Neoplasia Type 1

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Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the importance of duodenopancreatic neuroendocrine tumors (DP-NETs) as a key manifestation of multiple endocrine neoplasia type 1 (MEN1) and a critical determinant of long-term prognosis.
- Guide the diagnostic approach for patients with DP-NETs and MEN1, including when to initiate screening for asymptomatic individuals.
- Review the therapeutic management of patients with MEN1-related DP-NETs, including regional therapy, medical therapy, and observation

Significance of the Clinical Problem

MEN1 is an inherited endocrine tumor syndrome classically characterized by the occurrence of parathyroid tumors, DP-NETs, and anterior pituitary adenomas.¹ In addition to these hallmark manifestations, patients with MEN1 are

predisposed to developing a broader spectrum of endocrine and nonendocrine manifestations, including adrenocortical neoplasms, bronchial, and thymic NETs, as well as tumors of the skin and central nervous system. Most individuals with MEN1 harbor a detectable germline pathogenic variant in the *MEN1* gene on chromosome 11q13, which encodes the tumor suppressor protein menin. The prevalence of MEN1 is estimated to be between 1 in 20,000 and 1 in 40,000 individuals with equal sex distribution and no predilection for race or ethnicity.² DP-NETs are the second most common manifestation of MEN1 and demonstrate progressive age-related penetrance, affecting up to 80% to 90% of individuals by the seventh decade, with a mean age at diagnosis in the early forties.¹⁻³ The true prevalence is likely even higher, as many DP-NETs are small and undetectable on cross-sectional imaging.⁴ Historically, functional DP-NETs, such as insulinomas and gastrinomas, were thought to comprise most NETs in individuals with MEN1, but more recently—and likely due to better methods of detection—the prevalence of nonfunctional pancreatic NETs (NF-PNETs) has surpassed that of functional tumors. DP-NETs are the presenting manifestation of MEN1 in up to 20% of patients and are frequently identified

during screening of asymptomatic individuals with a known MEN1 genetic diagnosis.¹

In one study, more than one-third of 80 children and adolescents with MEN1 who commenced screening for manifestations before age 18 years were found to have DP-NETs.⁵ Consistent with previous studies, most patients (>70%) had NF-PNETs, with one-third having insulinomas and a small minority (<5%) having gastrinomas. Among patients with functional DP-NETs, those with insulinomas often present at a younger age, sometimes during their teenage years, while those with gastrinomas tend to present later in life, typically after age 30 years.^{6,7} DP-NETs remain the leading cause of death among patients with MEN1, although patterns of morbidity and mortality have evolved substantially over the past few decades. Historically, gastrinomas with complications related to Zollinger-Ellison syndrome (ZES) accounted for most deaths related to DP-NETs, often due to refractory peptic ulcer disease resulting in upper gastrointestinal hemorrhage and intestinal perforation.⁸ With the advent of proton-pump inhibitors (PPIs) that effectively control excess acid production, life-threatening complications of ZES have become rare. Presently, metastatic NF-PNETs account for most disease-related mortality. According to data from a nationwide French cohort study, the life expectancy of patients with MEN1 is estimated to be approximately 15 years shorter than that of the general population (70 years vs 85 years), although this gap appears to be narrowing over time.⁹ In the same cohort, 59% of patients required at least 1 surgical intervention for DP-NETs by age 75 years, with 17% and 3% undergoing at least 2 and 3 operations, respectively.

Discussion

Diagnosis

DP-NETs are typically diagnosed in individuals known to have MEN1 or through surveillance of at-risk family members. Less frequently, the initial presentation may be driven by a functional syndrome, such as hypoglycemia from insulinoma or symptoms from ZES secondary

to gastrinoma. Diagnosing DP-NETs requires radiographic visualization of the tumor(s) and, in cases of suspected functional tumors, selective biochemical/hormonal evaluation.⁴ Cross-sectional imaging usually identifies tumors larger than 2 to 3 mm, and both CT and MRI are sensitive methods.^{10,11} In individual patients, one modality may outperform the other, so imaging strategies should be tailored accordingly. In some cases, carefully performed CT imaging can detect lesions not well visualized on MRI, while in others, MRI may be superior. When using CT, multiphasic protocols are essential. Biphasic or triphasic contrast-enhanced studies improve lesion detection compared with monophasic (venous-phase-only) imaging, which may miss smaller lesions or fail to characterize larger tumors. Whether triphasic imaging confers a significant diagnostic advantage over biphasic protocols remains uncertain. Given the longer acquisition times and increased radiation exposure associated with triphasic CT, this approach is generally reserved for preoperative planning when detailed assessment of peripancreatic vasculature is required. For long-term surveillance, especially in younger patients, MRI is favored over CT to minimize cumulative radiation exposure. Histological confirmation, typically obtained via endoscopic ultrasound (EUS)-guided biopsy, is not required when the presentation and imaging findings are characteristic of DP-NETs.¹ Most lesions demonstrate slow linear growth kinetics over time. Rarely, however, tumor grade transformation may occur, resulting in more rapid growth. Accelerated tumor growth, especially if limited to a single lesion that grows asynchronously with other lesions, should prompt EUS evaluation with biopsy.

When a functional DP-NET is suspected, biochemical confirmation is essential. In patients with insulinoma, the diagnosis rests on documenting autonomous, endogenous insulin secretion, evidenced by inappropriately elevated levels of insulin, proinsulin, and C-peptide relative to the degree of hypoglycemia.¹² The optimal hypoglycemia cutoff needed for accurate diagnosis

is debated, although glucose levels below 45 mg/dL (<2.5 mmol/L) or 55 mg/dL (<3.0 mmol/L) are commonly used in clinical practice. In many cases, a 72-hour fast is required, although some experts advocate for shorter-duration tests.¹³

Accurate preoperative assessment of insulinomas is imperative for optimizing outcomes of regional therapy, such as resection or ablation, particularly because insulinomas can be multifocal in a minority of patients with MEN1. Localizing insulinomas can be challenging, although most are visible on cross-sectional imaging, such as CT or MRI, with careful attention to contrast timing.¹⁴ EUS can identify smaller lesions that are not seen on cross-sectional imaging and allows for tissue sampling via either fine-needle aspiration (FNA) or fine-needle biopsy (FNB).¹⁵ Insulinomas almost invariably express the GLP-1 receptor, a suitable target for nuclear imaging with GLP-1 receptor analogues, such as exendin-4, which bind the receptor with high affinity.^{16,17} However, GLP-1 PET imaging remains limited in availability, particularly in the United States.

ZES results from excessive gastrin secretion by functional DP-NETs. Excessive gastrin production stimulates gastric parietal cells, leading to marked acid hypersecretion and the characteristic symptoms of ZES. Abdominal pain and diarrhea are the most common symptoms, each occurring in up to 75% of patients, followed by symptoms of gastroesophageal reflux and peptic ulcer disease.¹⁸ Gastroduodenal perforation is much less common, especially since PPIs became available, but still occurs, often in patients who have not yet been diagnosed.

The diagnosis of ZES and gastrinoma requires confirmation of both the presence of a DP-NET and inappropriate gastrin production, manifested as elevated fasting gastrin levels.¹⁹ Although gastrin levels in patients with ZES typically run in the thousands, there is a substantial overlap with levels seen in patients with chronic atrophic gastritis and patients taking PPIs, both of which can cause secondary hypergastrinemia. In fact, gastrin levels in most patients with gastrinoma are under 10-fold the upper limit of normal, placing them within the range seen in other conditions

known to elevate gastrin.²⁰ Consequently, it is not uncommon to encounter patients with classic ZES who have only modest elevations in gastrin levels.²¹ In patients suspected of having gastrinoma and ZES, discontinuation of PPI therapy to estimate true gastrin production is not recommended due to the risk of bowel perforation from uncontrolled acid production. Secretin and calcium stimulation tests can improve diagnostic accuracy but are not widely available and are infrequently used in practice. Most gastrinomas arise from within the “gastrinoma triangle,” bounded superiorly by the confluence of the cystic and common bile ducts, inferiorly by the second and third portions of the duodenum, and medially by the neck and body of the pancreas.²² Although gastrinomas may arise from either the pancreas or duodenum, those associated with MEN1 most commonly originate in the duodenum and are frequently small and multifocal. Similar to insulinomas, most gastrinomas can be identified by a combination of high-quality cross-sectional imaging, including PET and EUS.²³

Screening

Current international clinical practice guidelines recommend routine screening for DP-NETs in individuals with MEN1. The most recent update, published in 2025, introduced several refinements aimed at reducing surveillance burden while maintaining sensitivity for clinically significant disease.¹ Notably, the suggested age to begin imaging surveillance for DP-NETs is now 10 to 15 years, compared with earlier guidelines that recommended starting before age 10 years. This change reflects the low incidence of clinically relevant DP-NETs observed in children younger than 15 years of age.¹⁻⁴ The updated guidelines also endorse MRI as the preferred routine screening modality (rather than CT, MRI, or EUS, as previously recommended) and deescalate imaging frequency from annually to every 2 to 3 years in asymptomatic individuals without known DP-NETs.¹ Because most DP-NETs are nonfunctional, screening strategies that rely solely on biochemical

markers are inadequate and fail to detect most tumors. Accordingly, the 2025 guidelines no longer advocate for routine measurement of nonspecific markers such as chromogranin A, pancreastatin, and pancreatic polypeptide due to limited sensitivity and specificity. Similarly, routine annual biochemical screening for insulinoma, including fasting glucose/insulin testing, is no longer emphasized; instead, evaluation is symptom-driven from age 5 years, with biochemical and imaging testing pursued only in the presence of hypoglycemic symptoms. However, annual measurement of fasting serum gastrin at surveillance visits is still recommended for adults.

Monitoring Patients With Small NF-PNETs

Most patients with MEN1 and NF-PNETs harbor small, multifocal tumors, most of which can be monitored without immediate intervention. Current guidelines recommend active surveillance for tumors 2 cm or smaller.¹⁻³ Cross-sectional imaging with either CT or MRI is typically repeated 6 to 12 months after the initial diagnosis of the DP-NET, and, if stable, annual imaging during the first few years of follow-up is reasonable, with subsequent intervals individualized based on tumor behavior. The 2025 MEN1 guidelines formalize this risk-adapted approach by endorsing the deescalation of imaging surveillance intervals for stable tumors. For lesions 2 cm or smaller that demonstrate growth of less than 1 mm per year, extending imaging intervals to every 1 to 2 years is considered appropriate. In contrast, larger lesions, high-grade tumors, or those exhibiting accelerated growth warrant closer monitoring. MRI is now recommended as the preferred long-term imaging modality for most patients because it avoids ionizing radiation. In contrast, functional imaging with somatostatin receptor PET and EUS, previously considered potential screening tools, is now generally reserved for specific clinical scenarios in which the results would meaningfully alter management, such as rapid growth, diagnostic uncertainty, or

preoperative planning. Symptoms of functional DP-NETs should prompt radiographic and biochemical evaluation if they occur outside the planned surveillance visits.

Management of MEN1-Associated DP-NETs

The management of MEN1-associated DP-NETs is inherently challenging due to their multifocal nature and the coexistence of functional and nonfunctional tumors within the same patient, each with its own malignant potential. Furthermore, unlike sporadic NETs, where surgical resection may be curative, MEN1 is characterized by a lifelong predisposition to tumor development within a genetically primed pancreas and duodenum. Accordingly, management strategies must balance oncologic control and control of hormone-mediated symptoms with minimization of intervention-related morbidity and preservation of pancreatic endocrine and exocrine function.

Surgical Resection

Although surgical resection remains a cornerstone of management, the optimal timing and extent of surgery for MEN1-associated nonfunctional pancreatic NETs remain controversial. Current consensus guidelines generally recommend resection for tumors measuring 2 cm or larger in greatest diameter and for smaller lesions that demonstrate significant interval growth. This treatment paradigm reflects multi-institutional data correlating tumor size with distant metastatic risk and evidence that many lesions smaller than 2 cm exhibit slow growth and can be safely observed with active surveillance, as outlined in the preceding text.^{1,2} However, recent data have challenged the strength of this association, with the observation that a subset of tumors smaller than 2 cm may still metastasize, indicating that size alone does not fully reflect underlying tumor biology.²⁴ Thus, there is an unmet need for noninvasive biomarkers to predict aggressive

behavior, which would help facilitate personalized treatment decisions.

Once the decision is made to operate on a DP-NET in a patient with MEN1, determining the optimal extent of index surgical resection remains a matter of debate. Procedures range from parenchymal-sparing procedures, such as enucleation, to more extensive formal resections, including pancreatoduodenectomy (Whipple procedure) or distal pancreatectomy. Earlier surgical philosophy favored aggressive resections, exemplified by the “Thompson” or “Ann Arbor” procedure, which combined distal pancreatectomy, enucleation of identified pancreatic head lesions, regional lymphadenectomy, and duodenotomy (in the setting of ZES).²⁵ This approach was promoted in hopes that preemptive comprehensive resection would achieve durable oncologic control. However, over time, experience from high-volume centers has shown that despite aggressive resection, recurrence and the need for reintervention remain frequent.²⁶ Moreover, substantial morbidity, including pancreatic exocrine insufficiency and pancreatogenic (type 3c) diabetes, occurs in a significant proportion of patients.²⁷ While total pancreatectomy theoretically eradicates the risk of malignancy, this approach is generally avoided as an index procedure unless dictated by diffuse advanced disease, due to its operative risks and profound metabolic consequences. A more conservative surgical strategy prioritizes minimal resection at the outset to preserve pancreatic function, with the plan to undertake additional organ-sparing procedures if there is recurrence. This strategy is supported by data showing comparable morbidity rates between primary and repeat resections, as well as observations that some patients may not require reoperation for decades after their initial surgery.²⁸

In contrast to NF-PNETs, there is greater consensus on the management of functioning DP-NETs in MEN1. Most experts recommend resection for localized insulinomas, VIPomas, glucagonomas, and somatostatinomas, given the morbidity associated with uncontrolled hormone excess. The management of gastrinomas, however, remains controversial. Since medical therapy

with PPIs usually controls acid hypersecretion effectively, the rationale for surgery in this setting is to reduce metastatic risk rather than control symptoms. However, most MEN1-associated gastrinomas are small, multifocal, and duodenal in origin, which may make a durable biochemical cure unachievable. For this reason, many centers favor a nonoperative approach unless tumors are 2 cm or larger. Conversely, some groups advocate a more aggressive surgical strategy when the biochemical diagnosis is unequivocal and distant metastases are absent, aiming to prevent future metastatic progression.²⁹

Systemic Therapy to Control Symptoms of a Functional DP-NET Syndrome

A minority of patients with MEN1 develop functional DP-NETs that cause a characteristic hormone-mediated syndrome, most commonly insulinoma and ZES, both of which can be life-threatening. Although surgical resection of clinically functional DP-NETs is recommended whenever feasible, not all patients have resectable disease or are suitable surgical candidates. In such cases, systemic therapy is often required to control symptoms.

The medical management of hypoglycemia in patients with insulinoma is covered in detail elsewhere; the principles of management are discussed in the following text.^{12,30,31} Patients with mild symptoms can often achieve adequate control with frequent meals and snacks, including bedtime snacks, rich in slow-digesting carbohydrates. Diazoxide is frequently used but is limited by troublesome adverse effects such as fluid retention, nausea, and anorexia. In our experience, most patients can be managed effectively without diazoxide. Somatostatin analogues (SSAs) can control hypoglycemic symptoms and tumor growth; however, in rare cases, they can paradoxically exacerbate hypoglycemia by suppressing the counterregulatory secretion of glucagon.³² Of the available SSAs, pasireotide may be the most effective at controlling hypoglycemia, although its use is limited by a high incidence of treatment-related hyperglycemia.³³ Glucocorticoids can offer transient relief from hypoglycemia, but adverse

effects preclude long-term use. Everolimus, an mTOR inhibitor, can control both tumor growth and hypoglycemia and has emerged as a useful tool in the management of patients with symptomatic hypoglycemia from insulinoma, especially in those with advanced disease.^{34,35} Radioligand therapy, typically with beta-emitters, such as ¹⁷⁷Lu-DOTATATE, has emerged as an effective and safe method for controlling both refractory hypoglycemia and tumor growth in patients with metastatic insulinoma and is generally reserved for patients with advanced, metastatic NETs.³⁶ Patients with severe, recurrent hypoglycemia may require hospitalization and intravenous dextrose infusion, and not infrequently, such therapy precludes discharge to home. Ersodetug, a humanized monoclonal antibody targeting the insulin receptor, represents a promising investigational therapy for patients with refractory hypoglycemia and is currently being evaluated in a prospective, randomized trial (trial ID: NCT06881992).³⁷

Systemic Therapy to Control Tumor Growth

Significant progress has been made in treating advanced NETs over the past decade; however, prospective clinical trials focused specifically on MEN1-associated DP-NETs remain limited. Broadly, systemic therapies for controlling tumor growth in MEN1-associated DP-NETs can be considered in 2 contexts: (1) treatment of localized disease and (2) treatment of advanced or metastatic disease.

Evidence guiding systemic therapy to control tumor growth in patients with MEN1-associated DP-NETs is sparse. SSAs, including longacting octreotide (octreotide LAR) and lanreotide, have demonstrated antitumor and symptomcontrol activity in advanced NETs outside the setting of MEN1. The PROMID and CLARINET randomized trials confirmed the antitumor efficacy of SSAs in gastroenteropancreatic NETs, although only CLARINET included patients with pancreatic NETs.³⁸ Several studies have evaluated SSAs in patients with MEN1 and DP-NETs, but only a few were prospective, and all were small.³⁹⁻⁴³ In a nonrandomized, prospective observational study

of 42 patients with 1 or more pancreatic NET 2 cm or smaller, 23 received lanreotide and 19 underwent active surveillance only.⁴¹ The primary objective was to compare progression-free survival, which was defined as a 20% or greater increase in the size of existing lesions that were 10 cm or larger at baseline and/or the appearance of new pancreatic lesions or nodal or distant metastases. Median progression-free survival was significantly longer in patients receiving lanreotide than in those undergoing observation (not reached vs 40 months). While these findings suggest biologic activity, the small sample size and nonrandomized design limit definitive conclusions. The efficacy of SSAs is supported by a systematic review of published studies, but because all are small and many have methodological limitations, it is difficult to draw firm conclusions about clinical utility.³⁹ The clinical benefit of preventing the growth of a tumor smaller than 2 cm is now known, and the cost implications of long-term therapy are significant. SSAs should not be considered standard therapy for patients with small but slowly progressive DP-NETs in those with MEN1, but they can be considered in highly select cases.

Systemic therapy other than SSAs has not been studied in patients with MEN1 with localized but progressive DP-NETs and is not recommended. Systemic therapy for advanced/metastatic NETs in patients with MEN1 should follow the same paradigms used in patients without MEN1. Further discussion of systemic therapy for advanced NETs is beyond the scope of this chapter, but multiple treatment guidelines are available.^{30,44,45}

Regional Therapy Other Than Resection

In patients with DP-NETs who are not suitable candidates for operative intervention, ablative and radiation therapies may be considered after careful multidisciplinary evaluation. Very limited data exist on regional therapy, other than resection, for MEN1-related DP-NETs, but there have been multiple recent reports on the utility of such interventions in patients with sporadic pancreatic NETs. EUS-guided ablation, either with ethanol

injection or other ablative methods such as radiofrequency ablation, has been shown to be safe and effective in patients with insulinoma and other pancreatic NETs, but outcomes appear inferior to those of minimally invasive resection.^{46,47} Duodenal NETs are usually not suitable for ablative therapy, but endoscopic resection is appropriate for carefully selected patients.^{48,49} External-beam radiotherapy has activity in well-differentiated NETs and can be considered for locally progressive tumors in patients with MEN1-related DP-NETs when other interventions are not feasible.⁵⁰ External-beam radiotherapy for functional NETs can effectively control symptoms, assuming the functional component of the malignancy is identified, and the lesion itself is safely included in the radiation field.⁵¹ Proximity to upper abdominal viscera, especially the duodenum, poses challenges for NETs in the pancreas and duodenum, and the risk of such therapy can outweigh any potential benefits. It is imperative that decisions regarding radiotherapy be made following a multidisciplinary discussion, and that treatment be delivered by an experienced team at a high-volume center.

Clinical Case Vignettes

Case 1

A 19-year-old man is brought to the emergency department after being found unconscious in his car. On arrival of emergency medical services, his plasma glucose concentration was 21 mg/dL (70–99 mg/dL) (SI: 1.7 mmol/L [3.9–5.5 mmol/L]). Intravenous dextrose was administered with prompt resolution of symptoms. One year ago, he experienced a similar episode of severe hypoglycemia requiring intravenous dextrose after being found unresponsive at home. At that time, the episode was attributed to low BMI, poor oral intake, and strenuous sports activities the night before.

CT of the abdomen with intravenous contrast reveals a 17-mm enhancing mass in the pancreatic body (*Figure 1*). A somatostatin receptor (SSTR) PET-MRI (⁶⁸Ga-DOTATATE PET-MRI) shows an intensely avid exophytic mass in the head/

Figure 1. Case 1 Abdominal CT



Abdominal CT (arterial phase) showing an enhancing mass in the head/neck region of the pancreas.

[Color—Print (Color Gallery page CG22) or web & ePub editions]

neck region of the pancreas without additional abnormalities (*Figures 2 and 3, following page*). His family history is notable for MEN1 affecting his father, paternal uncle, and grandfather. The patient has no persistent symptoms at the 4-week follow-up.

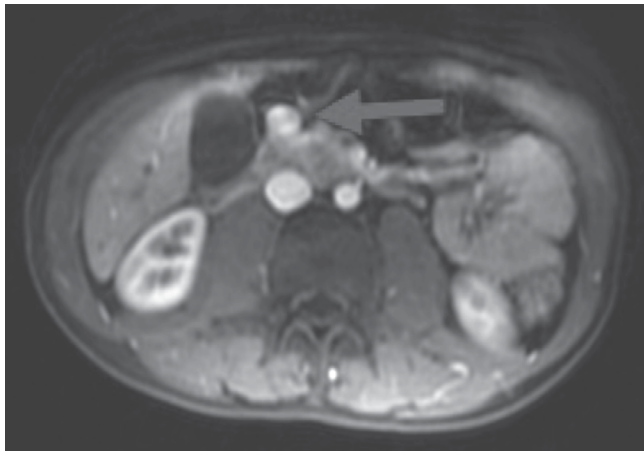
Which of the following is the most appropriate next step in this patient's management?

- Upper-endoscopic ultrasonography (EUS) with a biopsy of the pancreatic mass
- Admission to the hospital for a 72-hour fast to confirm insulin secretion resulting in hypoglycemia
- Referral to a surgeon with expertise in pancreatic surgery for consideration of resection
- Initiation of diazoxide followed by close observation
- Referral for EUS-guided ethanol ablation of the presumed insulinoma

Answer: C) Referral to a surgeon with expertise in pancreatic surgery for consideration of resection

This patient's presentation fulfills the Whipple triad, with documented symptomatic

Figure 2. Case 1 Abdominal MRI



Abdominal MRI (arterial phase) showing an enhancing mass in the head/neck region of the pancreas.

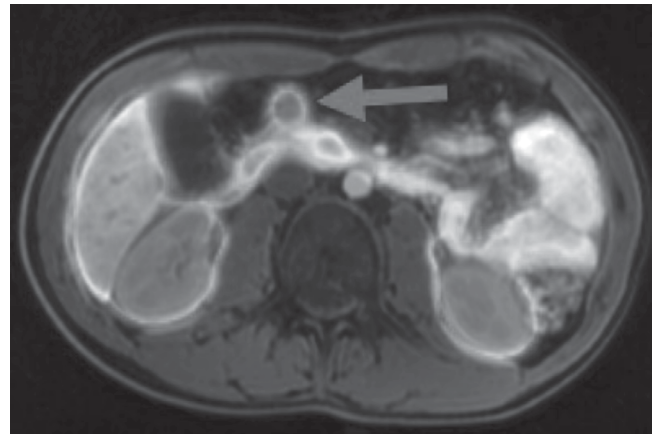
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hypoglycemia and prompt relief following intravenous glucose administration. In the setting of radiographic localization of a pancreatic lesion, 2 episodes of severely symptomatic hypoglycemia, and a strong family history of MEN1, the diagnosis of insulinoma is highly likely. Surgical resection is the definitive therapy and is indicated in medically fit patients with localized disease. While performing a biopsy is not unreasonable, this patient needs an intervention for the functional insulinoma to prevent further hypoglycemic episodes. Diazoxide would be reasonable, but because insulin secretion is very episodic in this patient, a more definitive therapy is indicated. EUS-guided ethanol ablation is useful in select cases, especially when resection is not feasible or the patient is not an operative candidate. Given this young man's excellent health, resection of the pancreatic NET is recommended.

Case 1, Continued

The patient undergoes an uneventful minimally invasive enucleation of the pancreatic NET and is discharged from the hospital after a short stay. He presents to the clinic to discuss surveillance plans. He has had genetic testing that confirmed a germline pathogenic variant in the *MEN1* gene. Interestingly, other family members with

Figure 3. Case 1 SSTR (⁶⁸Ga DOTATATE) PET-MRI



SSTR (⁶⁸Ga DOTATATE) PET-MRI showing an SSTR-avid mass.

[Color—Print (Color Gallery page CG23) or web & ePub editions]

MEN1 have had functional gastrinoma resulting in ZES, but he is the first in the family to have symptomatic insulinoma.

Which of the following is the most appropriate strategy to monitor for the development of DP-NETs?

- Annual laboratory testing (insulin, proinsulin, C-peptide, gastrin, chromogranin A) with imaging only if laboratory results are abnormal
- Annual laboratory testing (fasting gastrin) and cross-sectional imaging with MRI of the abdomen with intravenous contrast
- Annual SSTR PET-CT and laboratory testing (fasting gastrin)
- Annual upper EUS and laboratory testing (fasting gastrin)
- No further follow-up unless symptoms recur

Answer: B) Annual laboratory testing (fasting gastrin) and cross-sectional imaging with MRI of the abdomen with intravenous contrast

The most appropriate follow-up strategy for this patient is annual cross-sectional imaging of the abdomen with intravenous contrast, either MRI or CT. For younger individuals especially, we favor MRI over CT to avoid radiation exposure. For laboratory testing, no functional tumor markers

are needed beyond gastrin (which is even more important in this case, given the family history of ZES). Nonspecific tumor markers such as chromogranin A, pancreastatin, or pancreatic polypeptide lack sensitivity and specificity. Insulin, proinsulin, and C-peptide are uninformative unless the patient is having a hypoglycemic spell. Upper EUS provides excellent imaging of the pancreas but is invasive, requires deep sedation, and is generally not needed, but it could be considered if pancreatic imaging abnormalities appear over time. SSTR PET is not recommended for surveillance, given the limited data supporting its efficacy and the associated radiation exposure. Given the high-risk of tumor recurrence, recommending no follow-up is not appropriate.

Case 1, Continued

The patient remains well for 5 years without evidence of recurrence. Although the initial presentation was that of functional insulinoma, the functional status of pancreatic NETs—both those related to MEN1 and sporadic pancreatic NET—can change over time. Previously functional pancreatic NETs may become nonfunctional and vice versa.

In patients with metastatic, unresectable malignant insulinoma that is not amenable to regional therapy such as hepatic artery embolization, and with persistent hypoglycemia, which of the following systemic therapies offers the highest likelihood of durable control of both hormone-mediated symptoms and tumor progression?

- A. Somatostatin analogue, such as octreotide and lanreotide
- B. Everolimus
- C. Diazoxide
- D. Cabozantinib
- E. Radioligand therapy, such as ^{177}Lu -DOTATATE

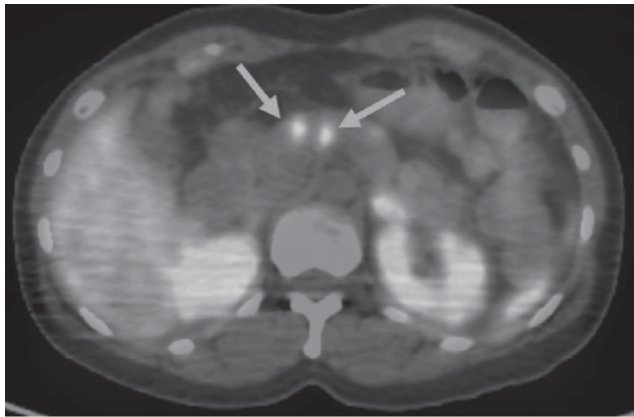
Answer: E) Radioligand therapy, such as ^{177}Lu -DOTATATE

In patients with metastatic malignant insulinoma, the goals of systemic therapy are to control both hypoglycemia and tumor growth. Regional therapy such as surgical debulking or liver-directed therapy (eg, hepatic artery embolization) is preferred when it is feasible, assuming the patient's health status allows. In patients in whom regional therapy is not feasible, systemic therapy can effectively control both the syndrome and tumor progression. Radioligand therapy targeting the somatostatin receptor, such as ^{177}Lu -DOTATATE, has emerged as a very effective option that controls hypoglycemia in more than 90% of patients, often resulting in tumor regression or stability that can last several years. While everolimus can effectively control hypoglycemia, the duration of tumor control is not as long as with radioligand therapy. Somatostatin analogues can control hypoglycemia but not as effectively as radioligand therapy (pasireotide may be the most effective to control hypoglycemia), but tumor control is not as durable as with radioligand therapy. Diazoxide can effectively control hypoglycemia, often with considerable adverse effects, but it does not control tumor growth. Cabozantinib effectively slows tumor growth in previously treated pancreatic NETs but does not help with hypoglycemia.

Case 2

A 35-year-old woman with a strong family history of MEN1 (affecting her mother, maternal grandfather, and multiple maternal relatives) presents for evaluation. She reports frequent loose stools and occasional diarrhea, up to 4 to 5 episodes daily, with intermittent heartburn. She takes no medications. A fasting serum gastrin concentration is 1120 pg/mL (reference range <100 pg/mL) (SI: 1120 ng/L [<100 ng/L]). An upper EUS reveals multiple small pancreatic masses, the largest measuring 11 mm. An SSTR PET-CT demonstrates at least 3 small pancreatic NETs, but the other lesions in the pancreas are likely below the PET's limit of detection (*Figure 4, following page*).

Figure 4. Case 2 SSSTR PET-CT



SSSTR PET-CT showing 2 foci of avidity in the pancreatic body.
 [Color—Print (Color Gallery page CG23) or web & ePub editions]

Which of the following is the most appropriate next step in this patient's management?

- Initiation of twice-daily PPI, monitoring of symptoms, cross-sectional imaging in 6 to 12 months, and measurement of fasting serum gastrin in 6 to 12 months
- Repeat upper EUS specifically for biopsy to confirm the NET diagnosis
- Referral to a surgeon experienced in pancreatic resections for consideration of removing the largest pancreatic NETs
- Initiation of a somatostatin analogue, such as octreotide or lanreotide
- Cross-sectional imaging in 6 to 12 months with no further evaluation

Answer: A) Initiation of twice-daily PPI, monitoring of symptoms, cross-sectional imaging in 6 to 12 months, and measurement of fasting serum gastrin in 6 to 12 months

This patient has multifocal pancreatic NETs with symptoms that are suggestive of functional gastrinoma with ZES. Also, her fasting plasma gastrin concentration is in the “gastrinoma range,” above 1000 pg/mL (>1000 ng/L), although there is an imperfect correlation between gastrin levels and symptoms of ZES. Given the presence of diarrhea and occasional heartburn in this clinical context, initiation of twice-daily PPI therapy is advised. After a week on omeprazole, 40 mg twice daily, the

diarrhea and the heartburn completely resolved, supporting the diagnosis of ZES. Repeat imaging without addressing ZES is not advised due to the risk of complications, including gastroduodenal perforation. Continuation of the PPI followed by repeat cross-sectional imaging in 6 to 12 months is reasonable. There is no need to repeat upper EUS to obtain a tissue sample, as the clinical picture strongly suggests a pancreatic NET. Somatostatin analogue therapy is not recommended at baseline, as most pancreatic NETs associated with MEN1 are very indolent. There is no role for surgical intervention at this point, given the small tumor size.

Case 2, Continued

This patient is monitored for 6 years on twice-daily PPI therapy with annual laboratory testing and abdominal MRI alternating with CT, as the pancreatic masses are challenging to visualize. She has no new symptoms or concerns suggestive of uncontrolled ZES. Gastrin levels fluctuate between 500 and 1200 pg/mL (500-1200 ng/L) during this period. MRI 7 years after the initial diagnosis shows a new 2-cm mass in the pancreatic tail, while the previously noted pancreatic masses remain unchanged (*Figures 5 and 6, following page*). The mass is confirmed to be avid on SSSTR PET-CT, suggestive of an NET. She has no new symptoms, and her gastrin concentration is 612 pg/mL (612 ng/L).

Figure 5. Case 2 CT of the Abdomen and Pelvis



CT of the abdomen and pelvis showing a pancreatic tail mass.
 [Color—Print (Color Gallery page CG23) or web & ePub editions]

Figure 6. Case 2 SSSTR PET-CT

SSSTR PET-CT showing an SSTR-avid pancreatic tail mass.

[Color—Print (Color Gallery page CG24) or web & ePub editions]

Which of the following is the best next step?

- A. Observation with repeat imaging in 6 months
- B. Consultation with a surgeon experienced in pancreatic resections for consideration of distal pancreatectomy as soon as possible
- C. Initiation of a somatostatin analogue given the avid SSTR expression of the pancreatic NET
- D. Repeat upper EUS with biopsy of the pancreatic tail mass
- E. Consideration of SSTR-targeting radioligand therapy, such as ^{177}Lu -DOTATATE

Answer: D) Repeat upper EUS with biopsy of the pancreatic tail mass

Repeat upper EUS is indicated in this situation. There has clearly been a departure from the very indolent course of the known pancreatic NETs, suggesting a more aggressive biology. An upper EUS revealed a well-differentiated grade 3 pancreatic NET with a Ki-67 index of 28%. Observation only would not be appropriate given the appearance of this mass since the last imaging study 12 months ago. Proceeding with distal pancreatectomy without confirming the diagnosis is not advised. Although not an MEN1-associated diagnosis, pancreatic adenocarcinoma presents in a similar manner. Systemic therapy with a somatostatin analogue or radioligand therapy is not appropriate without having a

biopsy-confirmed diagnosis in this situation. This patient was referred to a hepato-pancreato-biliary surgeon after staging and underwent an uneventful distal pancreatectomy. She unfortunately experienced metastatic recurrence and required systemic therapy. This case illustrates the uncommon risk of tumor grade progression in patients with MEN1 and DP-NETs. While most patients have a very indolent course with stability or minimal progression over time, patients rarely have tumor grade transformation with more aggressive clinical progression. In such cases, a biopsy for confirmation is almost always indicated.

Key Learning Points

- DP-NETs are the second most common manifestation of MEN1, with up to 90% of individuals being affected by age 70 years. As DP-NETs are the leading cause of death in patients with MEN1, accurate diagnosis and structured surveillance strategies and interventions, when indicated, are critical for optimal outcomes.
- Surveillance for DP-NETs is usually initiated between 10 and 16 years of age, but clinically relevant DP-NETs are uncommon before age 15 years. Abdominal imaging, preferably with MRI, is recommended in adults with MEN1. The use of nonspecific markers, such as chromogranin A, is not recommended. While EUS is more sensitive than cross-sectional imaging, it is not routinely needed because most DP-NETs detectable only by EUS are of questionable clinical relevance.
- Observation is recommended for most patients with NF-PNETs smaller than 2 cm; however, tumor size alone does not fully predict malignant potential, and validated biomarkers for aggressive biology are lacking.
- Annual imaging is appropriate for most patients undergoing observation for NF-PNETs, but in patients with small (≤ 2 cm) tumors that exhibit slow growth rates (<1

mm/y), less frequent surveillance (every 2 years) may be suggested.

- The surgical management of MEN1-associated DP-NETs requires balancing oncologic control with preservation of pancreatic endocrine and exocrine function. When surgical resection is considered, pancreatic parenchyma-sparing procedures are generally recommended if feasible (eg, enucleation or limited pancreatic resections). Resection should be considered for most patients with localized insulinoma, but patients with small gastrinomas can often be observed without surgical intervention, assuming that acid production is adequately controlled with PPIs.
- Systemic therapy is recommended for patients with advanced DP-NETs not amenable to

resection or other regional therapy. The selection of therapy is partly dependent on the presence of a functional NET syndrome, but somatostatin analogues are frequently chosen as first-line therapy. The role of somatostatin analogues in patients with progressive yet localized DP-NETs remains unclear but may be considered in select cases.

- Ablative therapies, such as ethanol or microwave ablation, can be considered for patients with small functional pancreatic NETs that are not suitable for resection. Other regional therapies, such as hepatic artery embolization of liver metastases and radiotherapy for localized DP-NETs, can be considered after discussion by a multidisciplinary tumor board.

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ADIPOSE TISSUE, APPETITE, OBESITY, AND LIPIDS

Lipedema at the Intersection of Endocrinology and Adipose Biology

José O. Alemán-Díaz, MD, PhD

Figure. Stages of Lipedema According to Progression of Fat Accumulation and Changes to Skin and Lymphatic System 3



Adapted from the Lipedema Foundation, lipedema.org

GLP-1–Based Therapies: Preparing Patients With Obesity for Long-Term Maintenance and Transition

W. Timothy Garvey, MD

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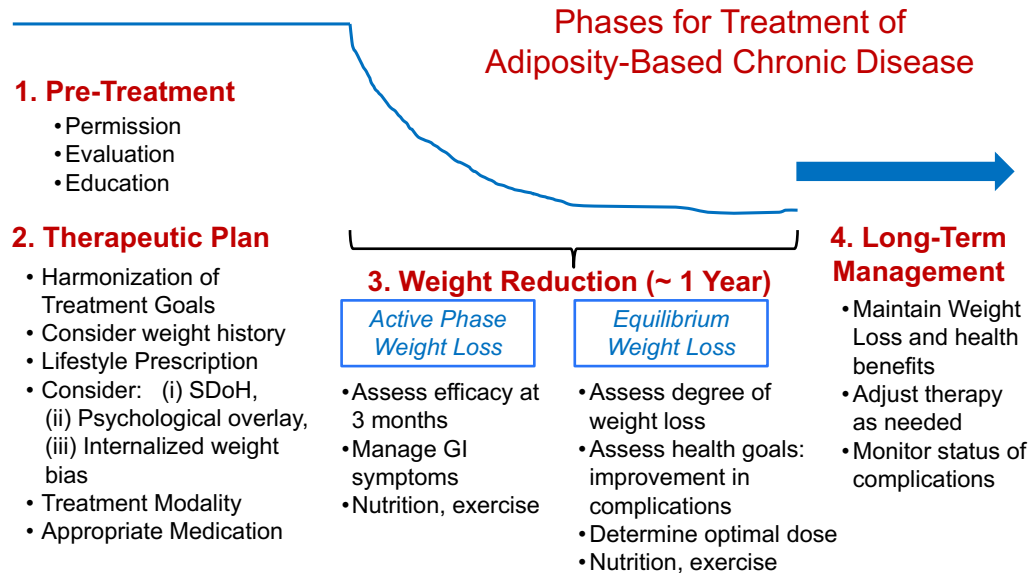


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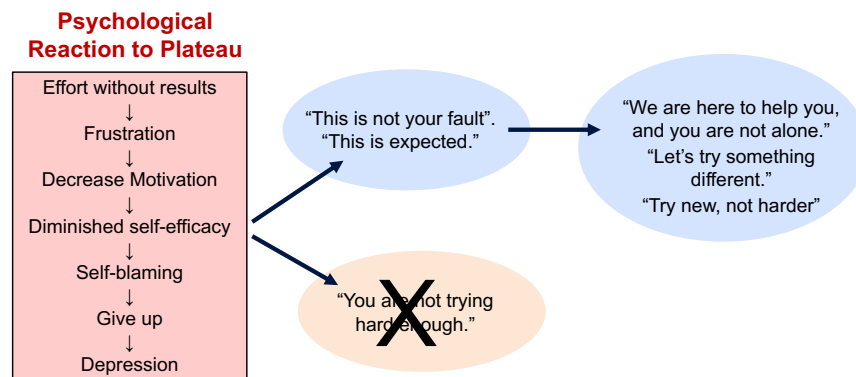
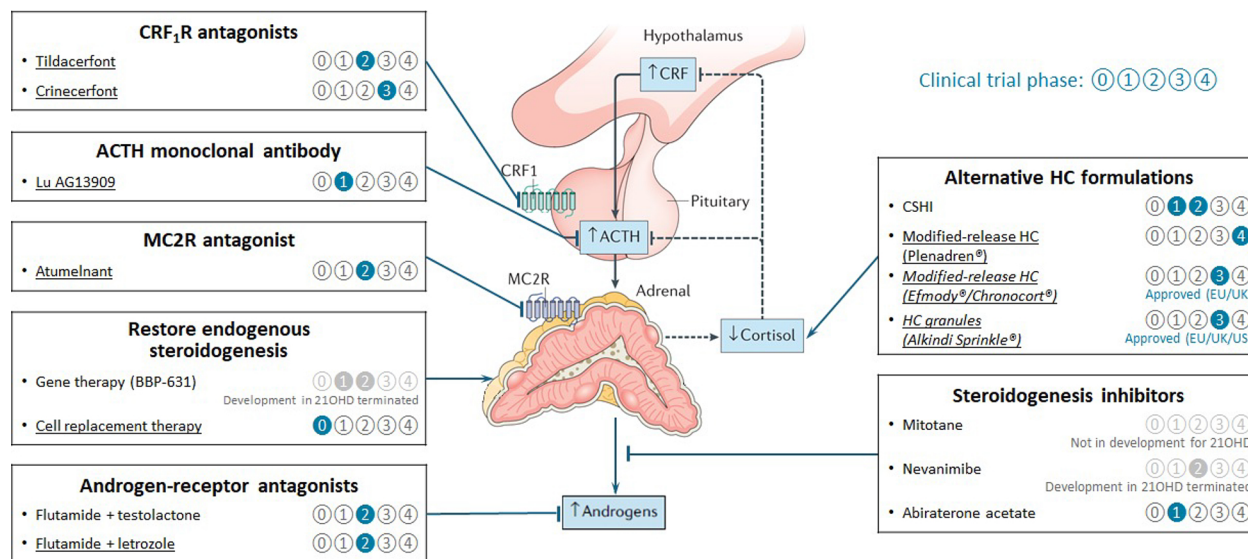


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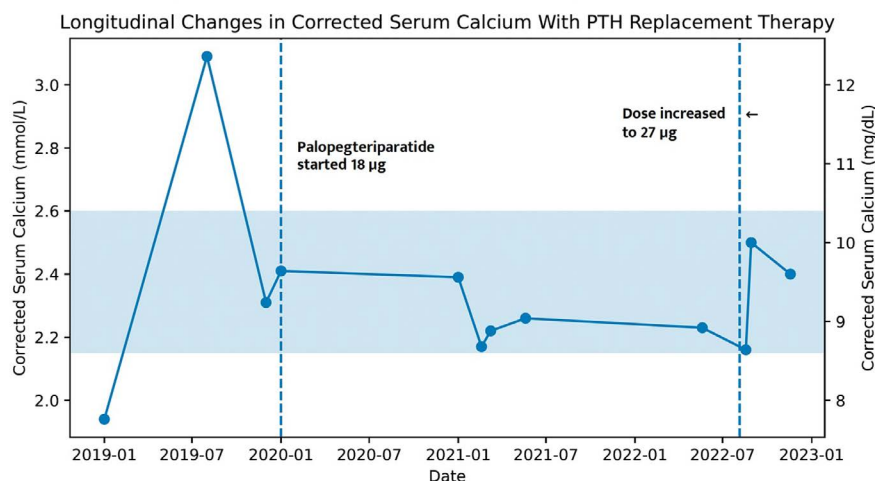
Since this publication, both Lu AG13909 (asdebart) and atumelnant have advanced to phase 2 and 3 trials in adults, with a phase 3 trial of atumelnant in children. Crinercerfont is in phase 3b and 4 trials, and the phase 1 trial of abiraterone acetate has been terminated. Reprinted from Sarafoglou K & Auchus RJ. *J Clin Endocrinol Metab*, 2025; 110(Supplement 1): S74-S87. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

BONE AND MINERAL METABOLISM

PTH Replacement Therapy for Chronic Hypoparathyroidism in Adults

Dalal S. Ali, MD, MSc, and Aliya A. Khan, MD

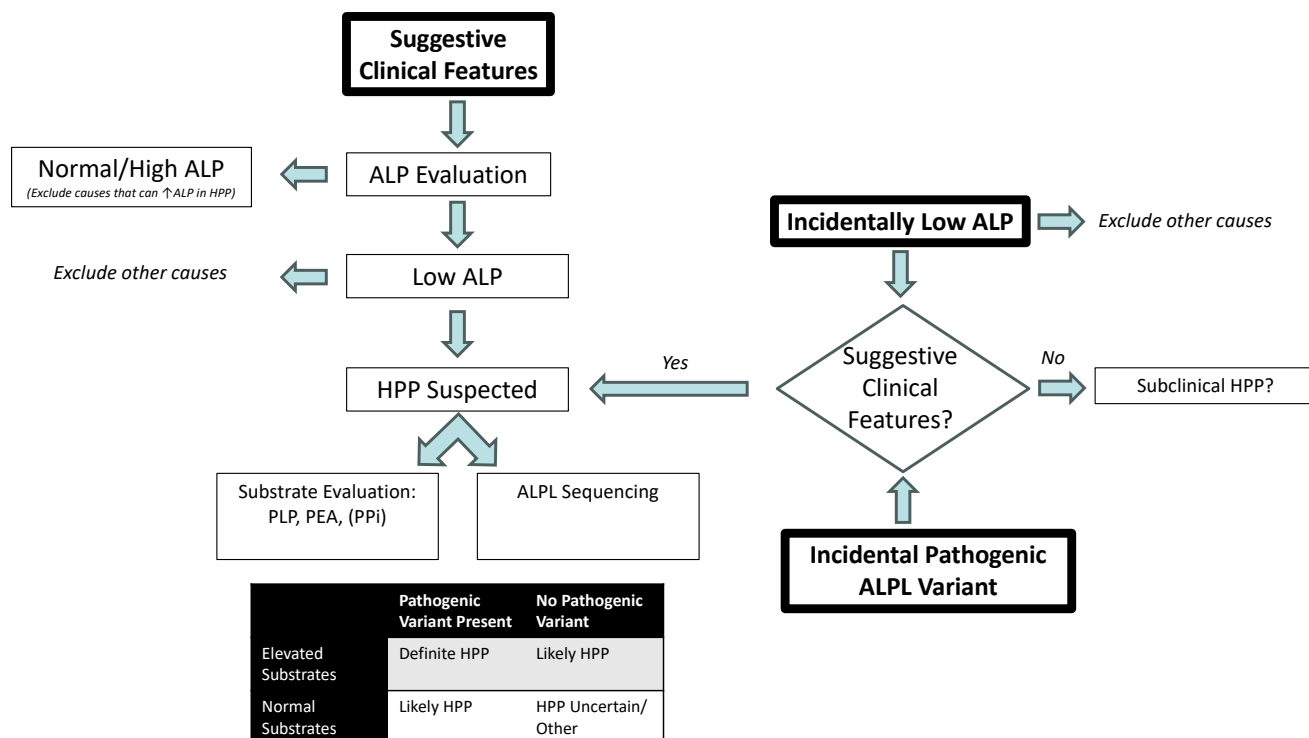
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Hypophosphatasia in Adults: Recognizing, Diagnosing, and Treating a Multisystem Disease

Juan Carl Pallais, MD, MPH

Figure. Diagnostic Pathways for HPP in Adults 113



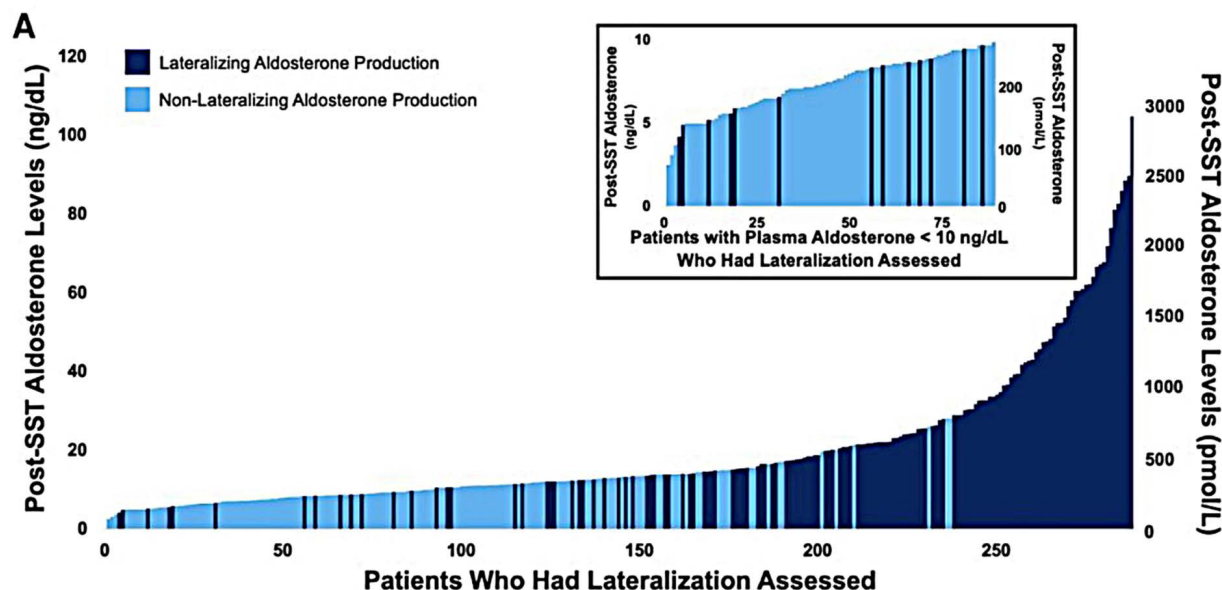
Adults with HPP may enter the diagnostic pathway through suggestive clinical features, incidentally identified persistently low ALP, or incidental detection of a pathogenic ALPL variant. Persistently low or low-normal ALP, after exclusion of secondary causes, should prompt evaluation for HPP, recognizing that total ALP may be masked by non-TNSALP isoenzymes or transient increases in bone or liver ALP. Diagnostic confirmation relies on parallel, rather than sequential, assessment of physiologic TNSALP substrates (PLP, PEA, PPi when available) and ALPL sequencing. Diagnosis integrates clinical, biochemical, and genetic data rather than any single parameter.

CARDIOVASCULAR ENDOCRINOLOGY

Interpreting Aldosterone and Renin: Tricks of the Trade

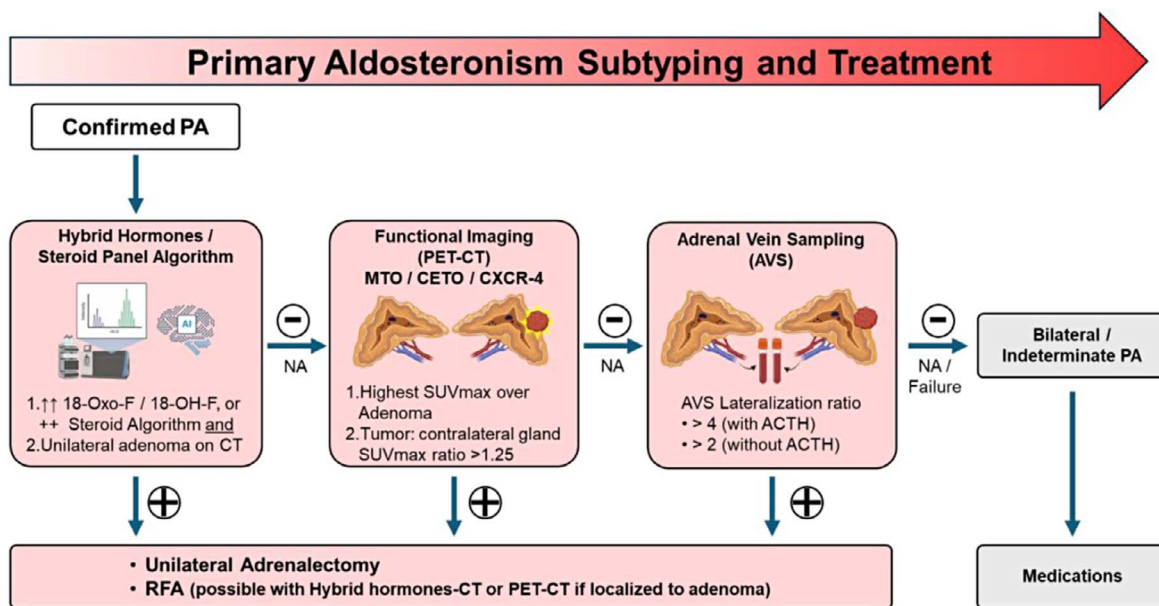
David Suphadetch Leungsuwan, MBBS, MMed, and Troy H. Puar, MBBS, PhD

Figure 1. Lateralization of Aldosterone Production and Treatment Decisions as a Function of SST 126



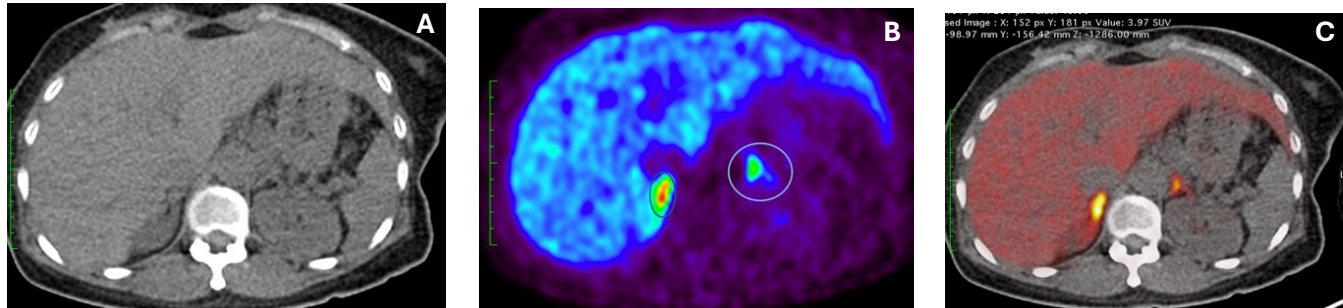
Lateralization of aldosterone production. Lateralization was assessed via AVS or imaging for a unilateral adrenal mass in patients with overt PA and hypokalemia; 143 of 288 patients (49%) were determined to have lateralizing PA. The inset depicts a magnified view of only those participants who had a post-SST aldosterone value less than 10 ng/dL (<277 pmol/L), wherein 13 of 89 patients (15%) had lateralizing PA (15%). Reprinted from Parksook WW et al. *J Clin Endocrinol Metab*, 2024; 109(9): 2220-2232. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.²³

Figure 2. Proposed Future Algorithm for Subtyping PA. 128



Abbreviations: NA, not available; SUVmax, maximum standardized uptake value. Current data suggest that each subtype test is highly specific. Hence, this algorithm recommends using them sequentially, from least to most invasive: hybrid hormone/steroid panel algorithm, molecular imaging, and AVS. *Clear lateralization for ¹¹C-MTO PET-CT uses an SUV_{max} ratio of greater than 1.25; thresholds with other radiotracers would differ. Reprinted from Ada E D Teo et al. *J Clin Endocrinol Metab*, 2025; 110(12): 3559-3568. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.³⁰

Figure 3. Case 3 Patient's Imaging..... 133

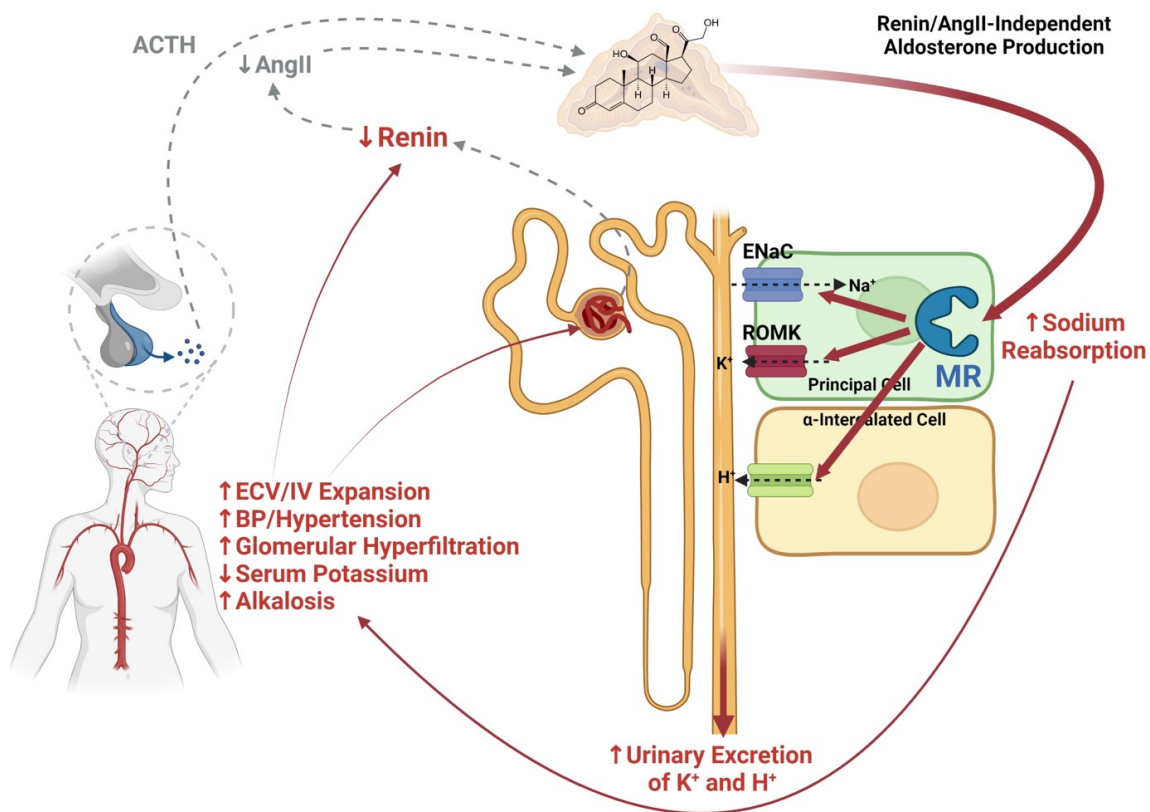


¹¹C-Metomidate PET-CT with Panel A, CT showing a right-sided 8-mm adrenal nodule; Panel B, highly PET-avid on PET with SUV_{max} of 47.3 compared with the left gland with an SUV_{max} of 24.2; Panel C, the fused images showing that the highest PET uptake is over the adrenal adenoma.

Evaluation and Management of Primary Aldosteronism

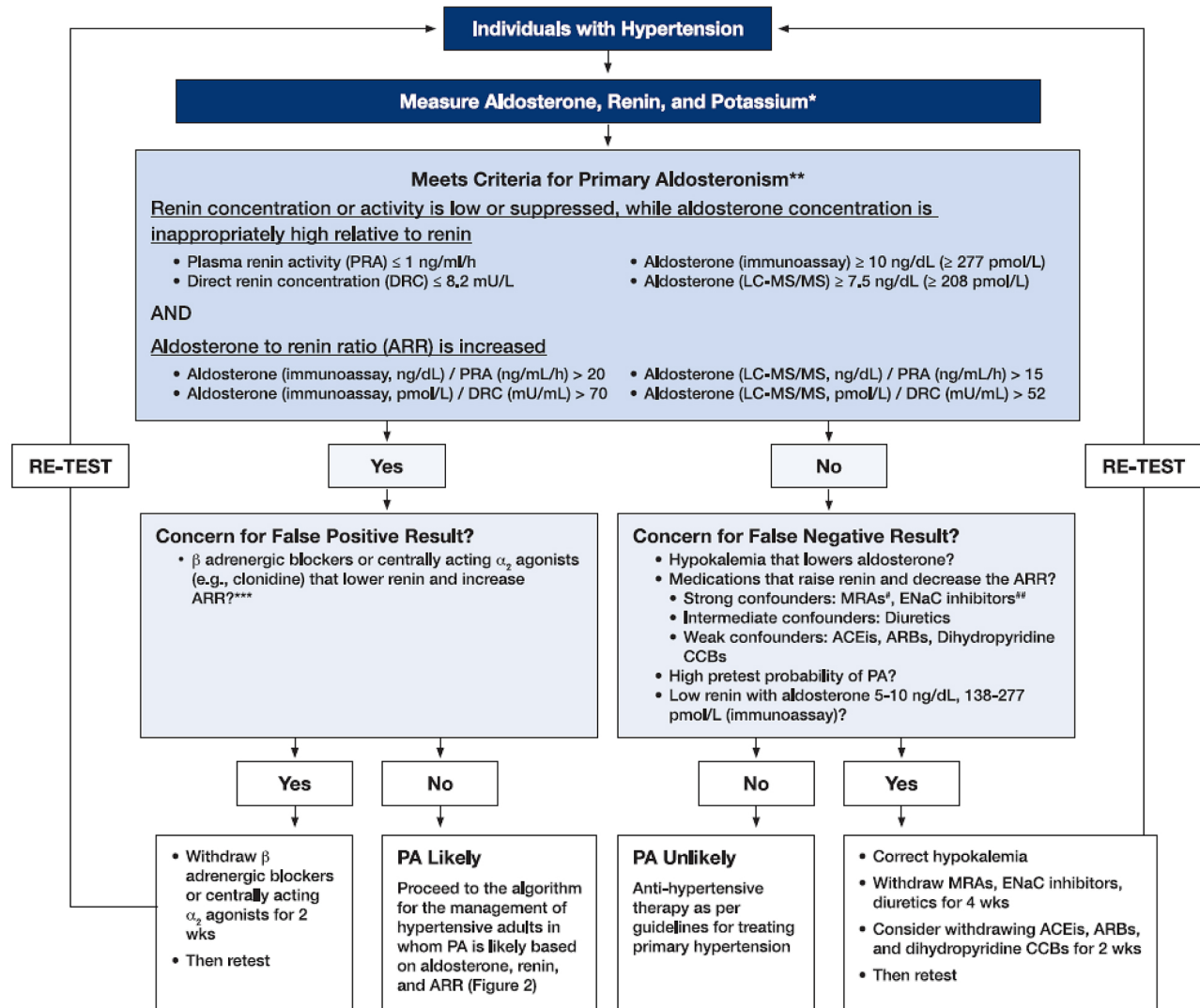
Anand Vaidya, MD, MMSc

Figure 1. Pathophysiology of Primary Aldosteronism 144



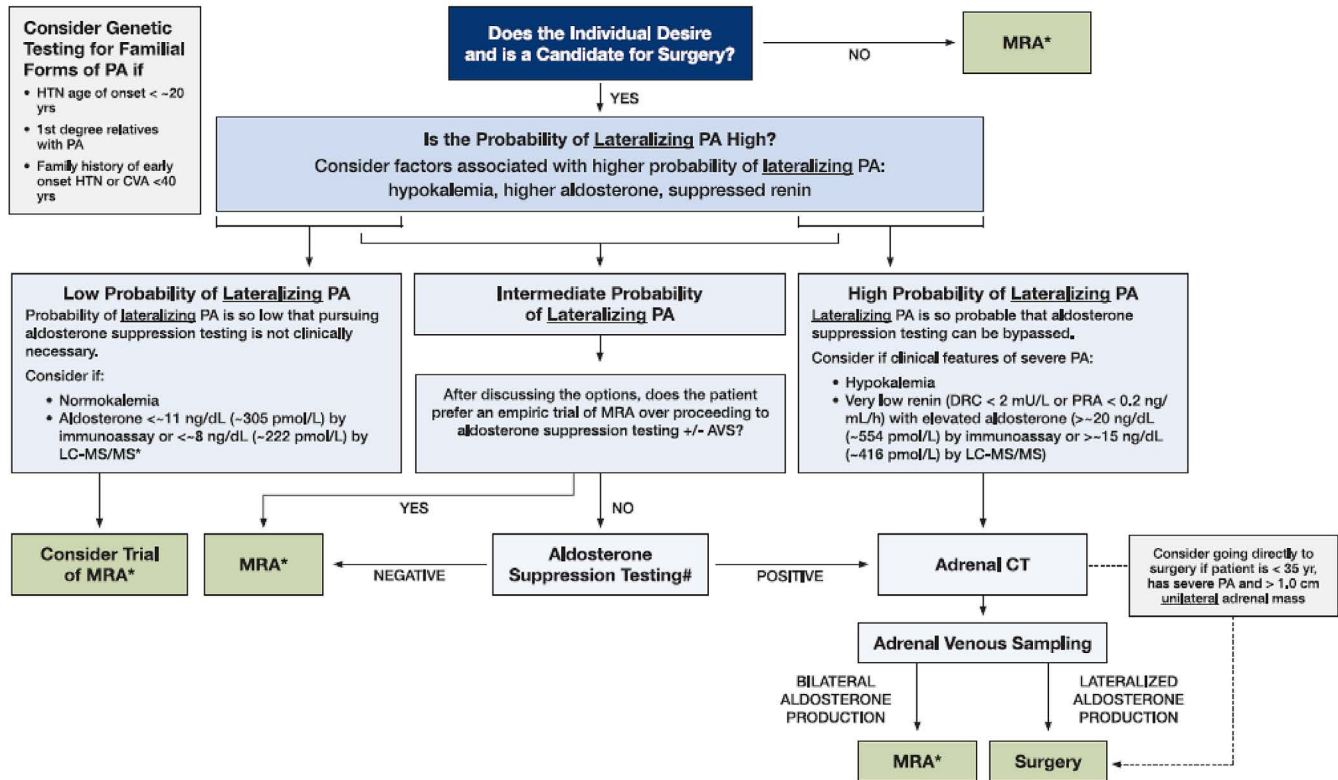
Aldosterone is physiologically regulated by the renin-angiotensin system, ACTH, and potassium. In primary aldosteronism, 1 or both adrenal glands contain foci of dysregulated aldosterone synthase expression that produce aldosterone independent of stimuli by angiotensin II and/or ACTH. This excess aldosterone production activates the MR in principal cells, even in volume-expanded states when renin and angiotensin II are suppressed, leading to inappropriate sodium reabsorption via ENaC and a commensurate excretion of potassium and hydrogen ions. This vicious cycle can induce the clinical manifestations of elevated blood pressure and hypertension, glomerular hyperfiltration, hypokalemia, and metabolic alkalosis. Abbreviations: Ang II, angiotensin II; BP, blood pressure; ECV, extracellular volume; ENaC, epithelial sodium channel; H⁺, hydrogen; IV, intravascular; K⁺, potassium; MR, mineralocorticoid receptor; Na⁺, sodium; ROMK, renal outer medullary potassium channel. Created with biorender.com. Reprinted from Hundemer GL et al. *Endocrine Reviews*, 2024; 45(1): 69–94. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

Figure 2. Screening for Primary Aldosteronism in Individuals With Hypertension 145



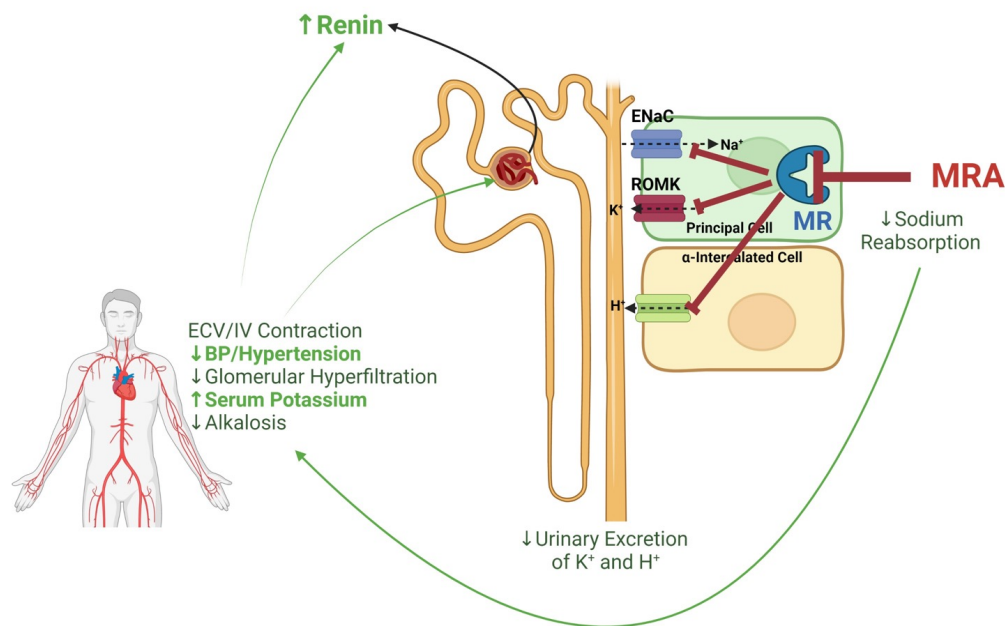
This figure outlines the screening process for primary aldosteronism (PA) in individuals with hypertension. *Blood is obtained in the seated position in the morning; ideally without venous stasis (release the tourniquet after venipuncture and wait at least 5 seconds before withdrawing blood) to avoid artifactual potassium increases. **The aldosterone, renin, and aldosterone-to-renin ratio (ARR) values provided in this figure are for guidance. However, as with many diagnostic tests based on continuous variables, sensitivity and specificity depend on the selected threshold. Aldosterone and renin levels are further influenced by individual variability, local laboratory assays, and other factors. Where possible, clinicians should rely on local laboratory cut points, as assays may vary. No cut point is perfect—each carries a trade-off between false-positive and false-negative results. Therefore, results should be interpreted in the context of the patient's pretest probability of primary aldosteronism, along with any interfering medications and conditions. ***Consider potential false-positive results induced by β -adrenergic blockers when aldosterone is <15 ng/dL (<415 pmol/L) by immunoassay and <10 ng/dL (<277 pmol/L) by liquid chromatography–tandem mass spectrometry. #Drospirenone in oral contraceptive pills is a mineralocorticoid receptor antagonist (MRA). ##Amiloride and triamterene are epithelial sodium channel (ENaC) inhibitors. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

Figure 3. Algorithm for the Management of Adults With Hypertension in Whom Primary Aldosteronism Is Likely. . 146



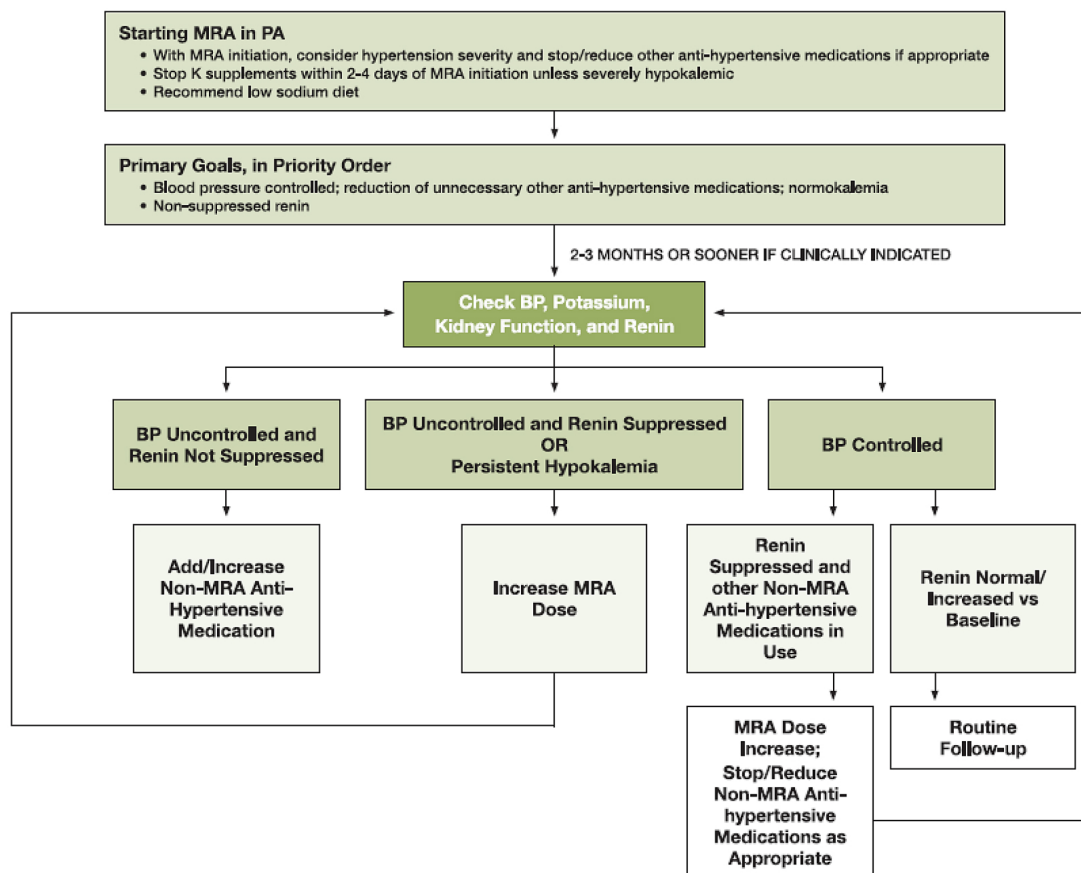
Patients likely to have primary aldosteronism (PA) who do not desire adrenalectomy or have contraindications to surgery can be offered mineralocorticoid receptor antagonist (MRA) therapy without further testing. MRA therapy is highly effective in PA. In addition, in studies of hypertensive individuals, MRAs consistently lower blood pressure more than alternative medication classes when renin is low or the aldosterone-to-renin ratio (ARR) is high. For patients interested in and capable of undergoing unilateral adrenalectomy, probabilistic and shared decision-making should be pursued. When the probability of lateralizing primary aldosteronism is low, patients can be offered MRA therapy without further testing. When the probability of lateralizing primary aldosteronism is high, cross-sectional adrenal imaging with CT and adrenal venous sampling can be performed to assess lateralization. When the probability of lateralizing primary aldosteronism is intermediate or uncertain, shared decision-making is advised. When possible, aldosterone-suppression testing may be considered to guide management in individuals willing and able to undergo testing. When interpreting the aldosterone-suppression test, one should consider the possibility of false-negative results. When aldosterone-suppression testing is not available or desired, MRA therapy can be initiated. Approximate values for aldosterone and renin are provided for guidance. *See Figure 5. Initiating and Monitoring MRA Therapy. #False negatives may occur, may be affected by local study conditions, and should be considered when deciding whether to proceed with adrenal venous sampling. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

Figure 4. Biomarkers of Optimal Medical Therapy for Primary Aldosteronism..... 149



Through blockade of the interaction between aldosterone and the MR in the principal cell of the distal nephron, MRAs decrease ENaC-mediated sodium reabsorption. This, in turn, decreases volume expansion and urinary excretion of potassium and hydrogen ions. If the degree of MR blockade is sufficient to cause intravascular volume contraction and relative kidney hypoperfusion, renin secretion from the juxtaglomerular cells will rise. Thus, a rise in renin, along with a lowering of blood pressure and normalization of serum potassium, serves as a biomarker of adequate MR blockade in primary aldosteronism. In bold are the key biomarkers that reflect optimized medical therapy in primary aldosteronism: normalization of blood pressure and serum potassium, and a rise in renin. Abbreviations: BP, blood pressure; ECV, extracellular volume; ENaC, epithelial sodium channel; H⁺, hydrogen; IV, intravascular; K⁺, potassium; Na⁺, sodium; ROMK, renal outer medullary potassium channel. Created with biorender.com. Reprinted from Hundemer GL et al. *Endocrine Reviews*, 2024; 45(1): 69–94. © The Authors. Published by Oxford University Press on behalf of the Endocrine Society.

Figure 5. Initiating and Monitoring MRA Therapy..... 150



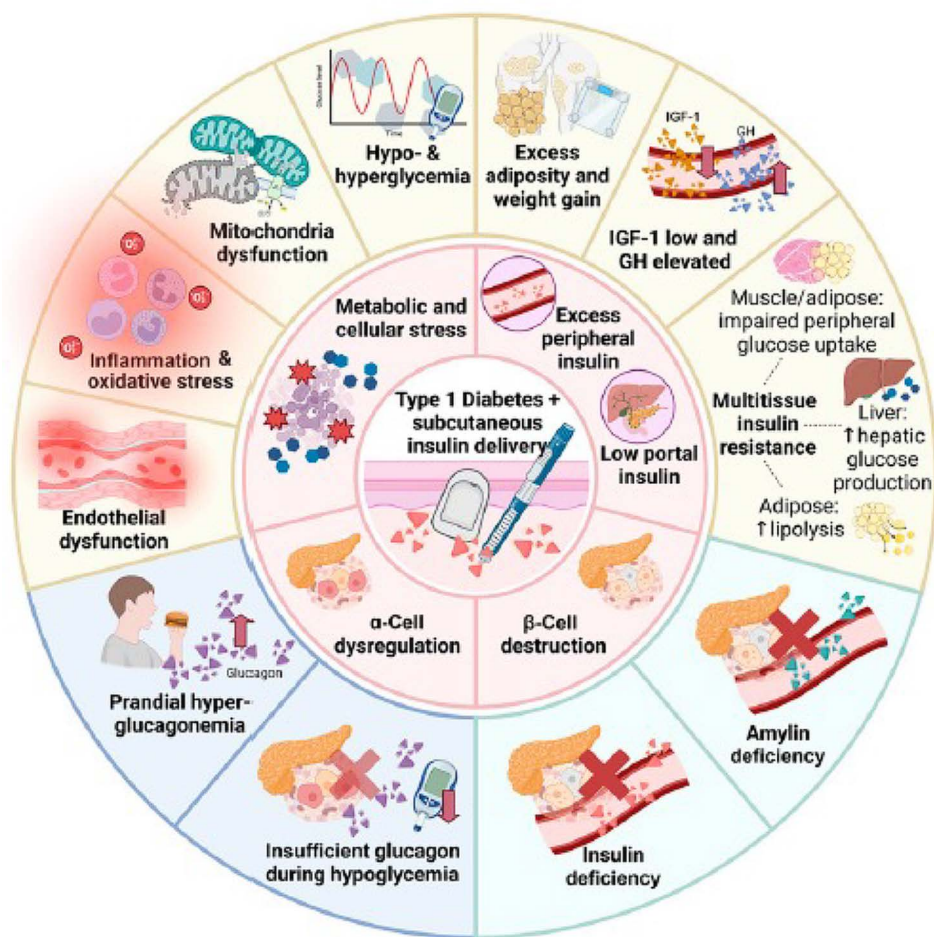
This is a general guide, and interpatient responsiveness to MRA dosing varies widely. MRA initiation and titration are often multistep processes. Each MRA adjustment is followed by assessment of blood pressure (BP) and biochemical response, then reentry into the treatment algorithm as appropriate. The primary therapeutic goal is BP control. The secondary goal is normokalemia. Measuring renin (as a marker of MR blockade) may assist in the process of MRA dose titration for achieving these goals and possibly reduce other non-MRA antihypertensive drugs. (1) Clinicians may start MRA at a relatively low dosage (spironolactone, 12.5-25 mg daily, or eplerenone, 25 mg daily or twice daily). Medically complex or frail individuals, and those at risk for MRA-drug interactions (eg, with an ACE inhibitor or ARB), may need careful monitoring. For individuals with more severe primary aldosteronism, especially with profound hypokalemia, a higher initial dosage could be considered (spironolactone, 50 mg daily, or eplerenone, 50 mg twice daily). (2) All individuals should have routine measurement of serum electrolytes, kidney function, and renin within 2 to 3 months of starting MRA therapy; more frequent serial measurements may be needed in those with prior severe hypokalemia or kidney impairment. Some panelists recommend inquiring about dietary sodium or measuring 24-hour urinary sodium at baseline and periodically during follow-up to track dietary salt restriction; a sodium target <85.5 mmol/d is recommended (representing <5 g/d salt intake). (3) MRA dosage changes to target BP control should occur at 8- to 12-week intervals, and the full drug effect may take up to 3 months in more severe forms of primary aldosteronism. Typical dosages required to de-suppress renin are variable and likely higher than dosages used empirically as add-on therapy for resistant hypertension; most individuals achieve renin de-suppression with spironolactone dosages (or spironolactone dosage equivalents) between 50 and 100 mg daily. Spironolactone may be increased in 25- to 50-mg increments, and eplerenone in 25- to 100-mg increments. With each MRA dosage change, repeat assessments of electrolytes, kidney function, and renin are recommended 2 to 3 months later. When possible, consider off-titration of other antihypertensive agents. Once renin is de-suppressed and further BP reduction is required, other non-MRA antihypertensive agents should be added or uptitrated. If BP is controlled on MRA monotherapy, there is insufficient evidence to support further increases in MRA dosage based solely on low renin levels. (4) Normalization of serum potassium usually occurs, even with lower-dosage MRAs, in the first 3 to 5 days, so it is reasonable to reduce or discontinue any potassium supplements 2 to 4 days after MRA initiation in all but the most severe hypokalemic cases. Individuals who require ongoing potassium supplementation require frequent, careful monitoring. Dietary salt restriction is a critical component of assessing the response to MRA therapy; individuals should be explicitly instructed in and assisted with dietary salt-reduction strategies. An ongoing high-salt diet is a very common reason for apparent nonresponse to MRA therapy. (5) Glomerular filtration rate (GFR) may decrease in individuals with primary aldosteronism on introduction of targeted medical therapy or with successive titration of MRA. The time course of change may be over days to weeks and, in most cases, represents a marker of treatment efficacy rather than an adverse effect. The natural history of an appropriate treatment-induced decrease in GFR is usually one of eventual long-term stability, suggesting a renal-sparing effect of effective MRA therapy. If kidney function progressively declines, consider referral to nephrology and discontinuation of ACE inhibitors or ARBs. (6) Gynecomastia from spironolactone is dose-related and may appear as early as 1 to 2 months into therapy, but more commonly after ≥6 months of treatment. In some cases (especially in younger males), reducing the dosage to ≤50 mg daily resolves gynecomastia. Some men may request a switch to a more selective MRA, such as eplerenone or other new MRA agents; amiloride is an alternative option. This almost always allows complete resolution of gynecomastia if it has not yet progressed to a large size. (7) Routine follow-up after MRA dose optimization should generally consist of blood pressure monitoring and annual measures of potassium and kidney function. Patients with chronic kidney disease or other risk factors for impaired kidney function/electrolyte disorders (eg, combination MRA and ACE inhibitor/ARB drugs) should undergo biochemical monitoring more frequently. Routine repeat renin measures are not necessary unless re-entering the MRA titration algorithm due to incomplete BP/potassium control. Reprinted from Adler, GK et al. *J Clin Endocrinol Metab*, 2025; 110(9): 2453–2495. © The Endocrine Society. Published by Oxford University Press on behalf of the Endocrine Society.

DIABETES AND VASCULAR DISEASE

Use of Adjunctive Glucose-Lowering Therapies to Target Cardiometabolic Risk in Type 1 Diabetes

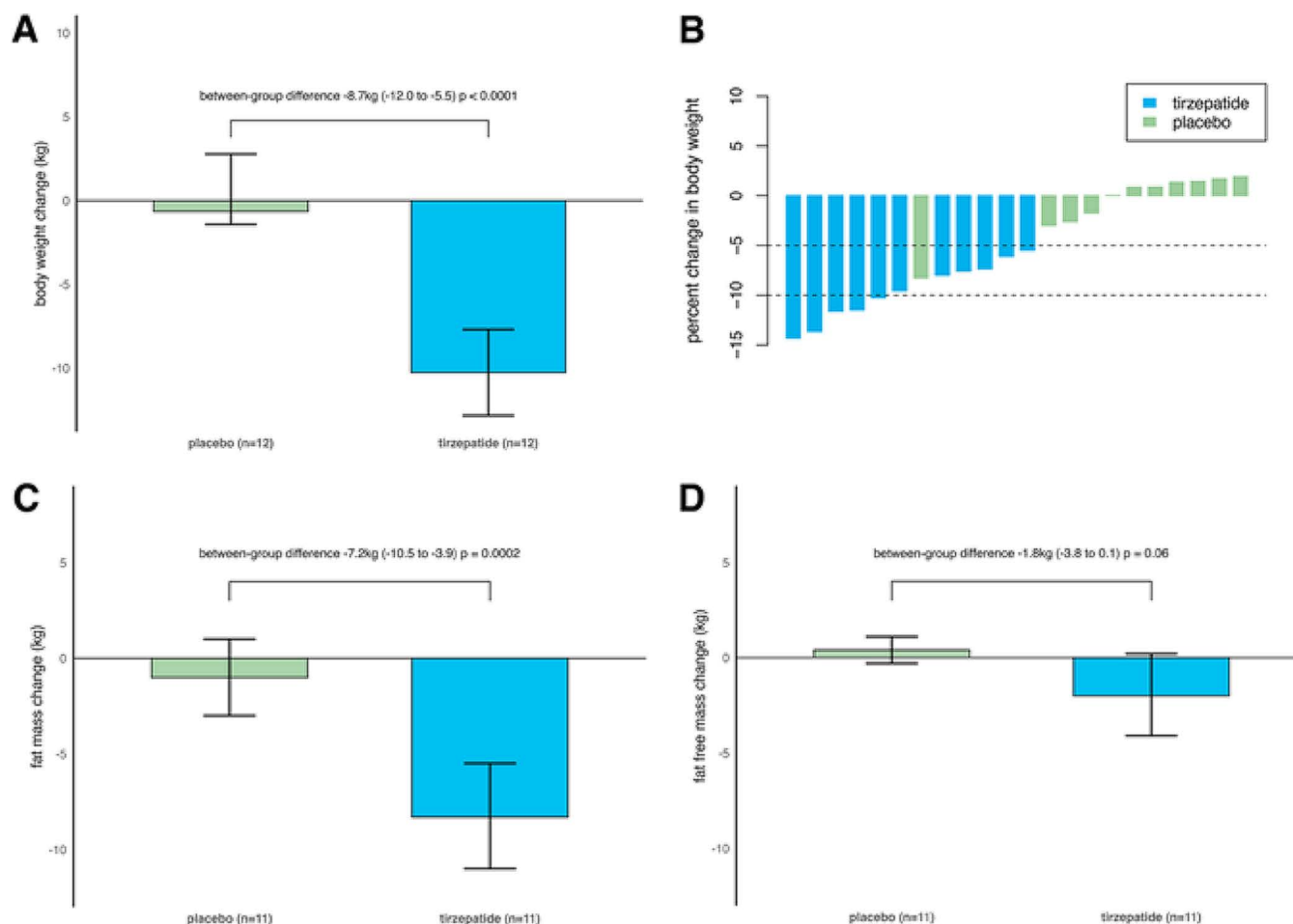
Jerry R. Greenfield, MD, PhD

Figure 1. Pathophysiological Contributors to Metabolic Dysfunction and CVD in T1D 180



Multiple pathophysiological contributors to metabolic dysfunction and CVD in T1D. Reprinted from Snaith JR et al. *Diabetes Care*, 2025; 49(1): 7-21. © by the American Diabetes Association.

Figure 2. Effect of Once-Weekly Tirzepatide on Body Weight and Composition in Adults With T1D 184



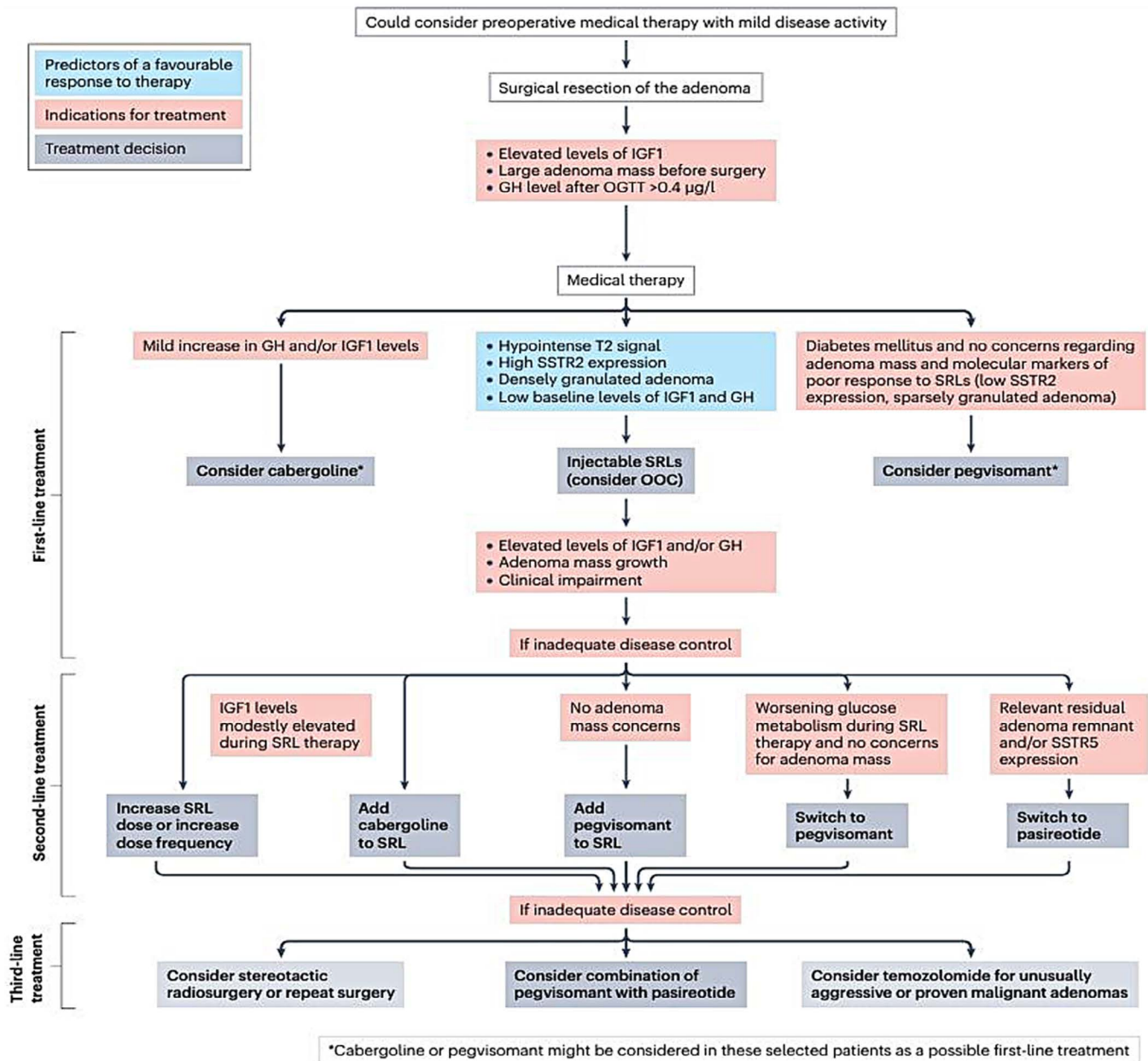
Effect of once-weekly tirzepatide compared with placebo on body weight (primary outcome) and body composition in adults with type 1 diabetes. *Panel A*, The change from baseline in body weight at 12 weeks as assessed by ANCOVA, adjusted for baseline, with multiple imputation for missing data at 12 weeks. *Panel B*, Participant-level percentage change in body weight ordered on the x-axis from greatest decrease to increase, plotted by treatment group. All participants randomly assigned to tirzepatide experienced a $\geq 5\%$ decrease in body weight, and 45% experienced $\geq 10\%$ over the 12-week treatment period, compared with 9% and 0% in the placebo group. *Panel C*, Change in fat mass. *Panel D*, Change in fat-free mass. Error bars represent the 95% CI. Reprinted from Snaith JR et al. *Diabetes Care*, 2025; 49(1): 161-170. © by the American Diabetes Association.

NEUROENDOCRINOLOGY AND PITUITARY

Current Approach to Acromegaly Care

Lisa Nachtigall, MD

Figure 1. Pituitary Society Acromegaly Consensus. 238



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Diagnosis and Management of Silent Pheochromocytoma and Paraganglioma

Christina Pamporaki, MD, PhD

Figure 1. Pathways of Catecholamine Synthesis and Storage 254

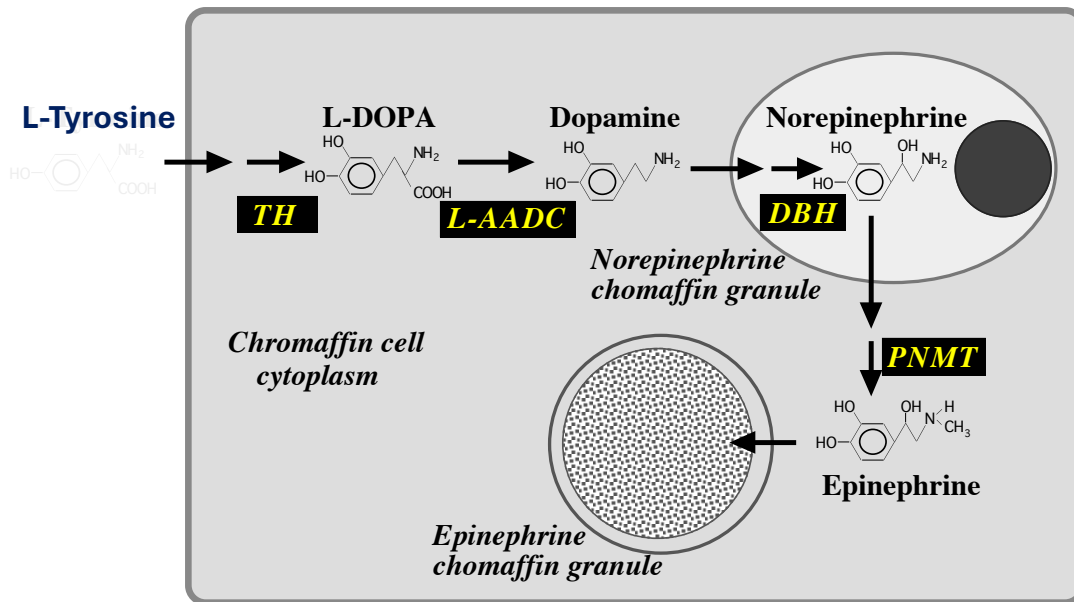


Figure 3. Workflow for the Management of Patients With Small Biochemically Negative PPGL 257

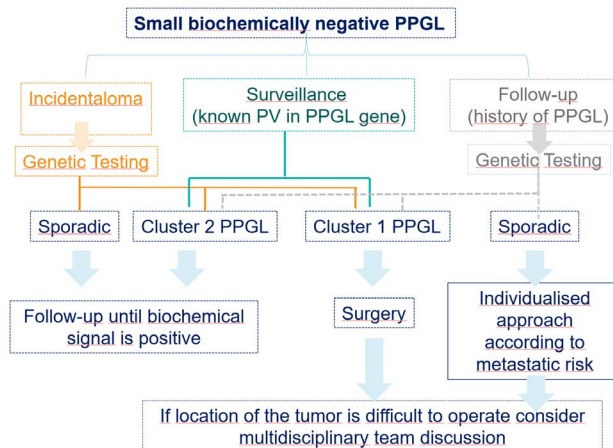
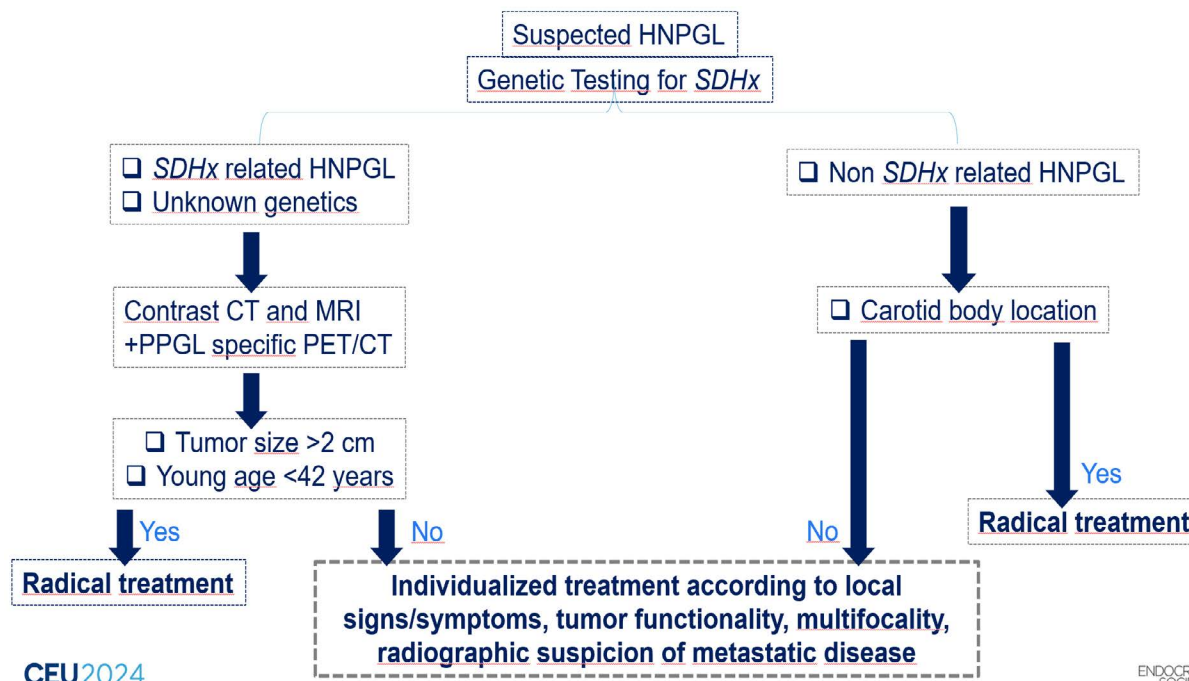


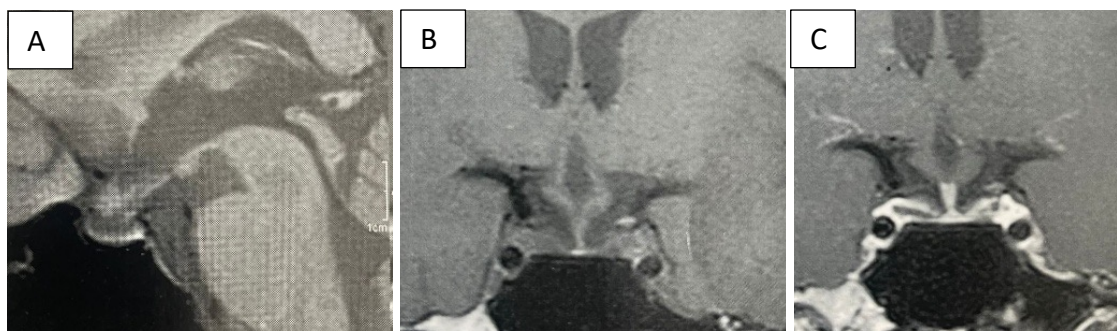
Figure 4. Workflow for Managing Patients With Nonfunctional HNPGL..... 258



A Structured Diagnostic Approach to Patients With Hypotonic Polyuria

Beatriz Santana Soares, MD, PhD, and Juliana Beaudette Drummond, MD, PhD

Figure 2. Sellar MRI in the Early Postpartum Period. 267



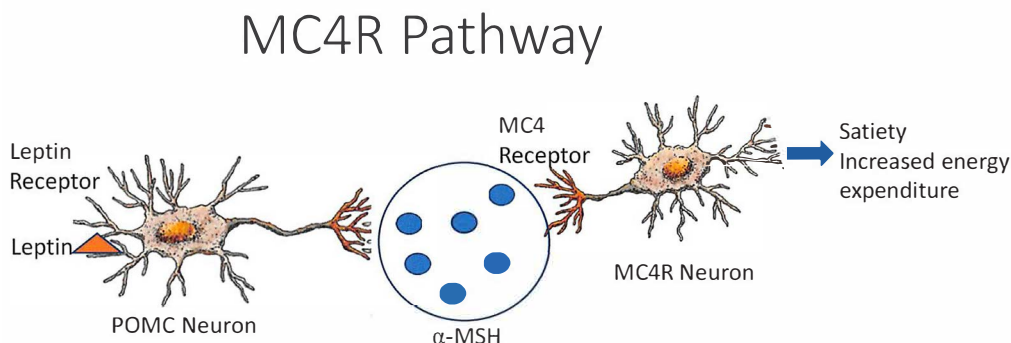
Panel A, Sagittal T1-weighted image demonstrating reduced pituitary gland volume and a preserved posterior pituitary T1 hyperintensity ("bright spot"). Panel B, Coronal T1-weighted image. Panel C, Coronal postcontrast T1-weighted image showing homogeneous pituitary enhancement without a focal sellar lesion.

PEDIATRIC AND ADOLESCENT ENDOCRINOLOGY

Management of Hyperphagia in Prader-Willi Syndrome and Other Monogenic Obesity Syndromes

Jennifer Miller, MD, MS

Figure 1. Melanocortin-4-Receptor Pathway. 291

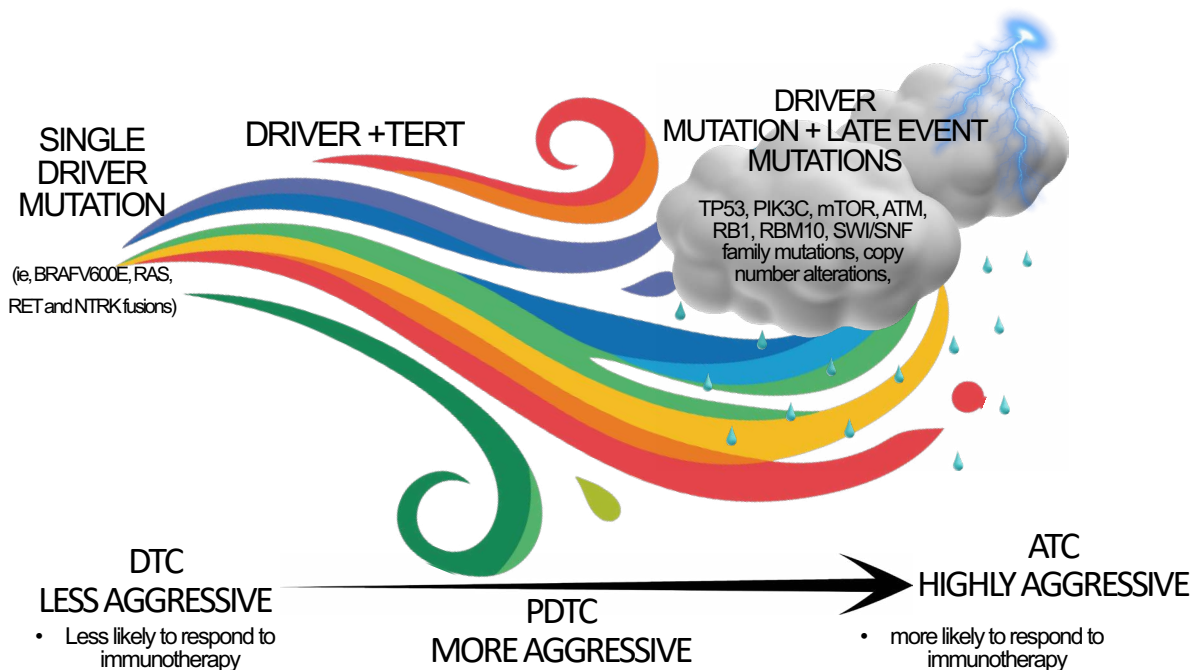


THYROID BIOLOGY AND CANCER

Recent Advances in the Management of Anaplastic Thyroid Cancer

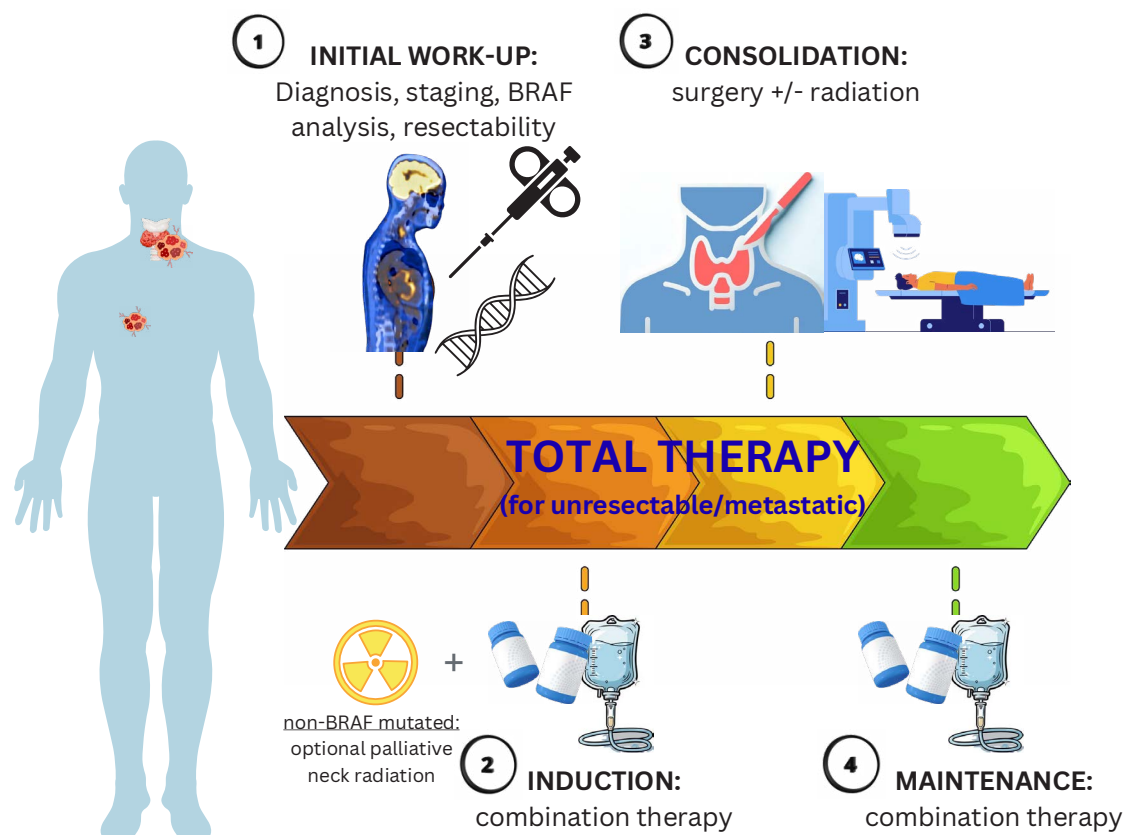
Maria E. Cabanillas, MD

Figure 1. Transformation of DTC to More Aggressive Thyroid Cancer (Poorly Differentiated and ATC) 327



The more aggressive forms of follicular-derived thyroid cancers are derived from DTC by acquiring late-event variants in genes such as TP53. These tumors also become more responsive to checkpoint inhibitor therapy as they transition to ATC. Abbreviations: DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer.

Figure 2. Total Therapy for Patients With Unresectable or Metastatic Disease 328

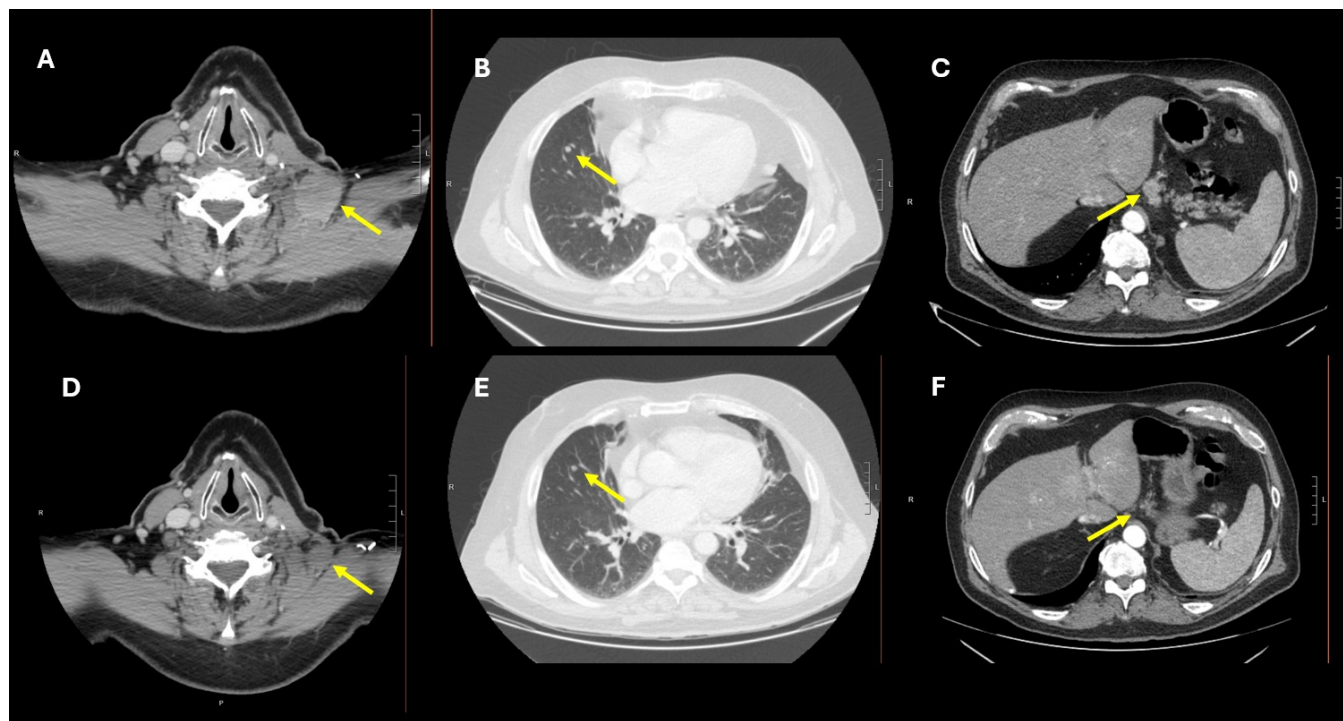


Patients with stage IVB unresectable or stage IVC disease should be fully staged and evaluated for the *BRAF* V600E variant (step 1). If the patient's tumor has the *BRAF* V600E variant, they should begin the Induction Phase (step 2) with dabrafenib/trametinib + pembrolizumab (when available). Patients without the *BRAF* V600E variant should be considered for Induction (step 2) with palliative radiation followed by lenvatinib/pembrolizumab. If the patient has a contraindication to lenvatinib, dual immunotherapy with ipilimumab/nivolumab can be considered. Restaging scans should be performed regularly (every 2 to 3 months) to determine if the patient is responding to therapy and to evaluate whether the primary tumor is resectable. In a patient with an excellent response throughout, removal of the primary tumor during the Consolidation Phase (step 3) could be considered within the first 6 months. Postoperative radiation should be discussed in a multidisciplinary forum, but this is often reserved for patients without metastatic disease, as targeted therapy is held during radiation. Finally, the Maintenance Phase (step 4) should be started soon after surgery ($\pm$ radiation). Patients who cannot undergo surgery may skip Consolidation and proceed directly to Maintenance (step 4), which consists of 1 to 2 years of PD-1 checkpoint inhibitor therapy, followed by indefinite continuation of the targeted therapy.

Targeted Therapy in Advanced Thyroid Cancer

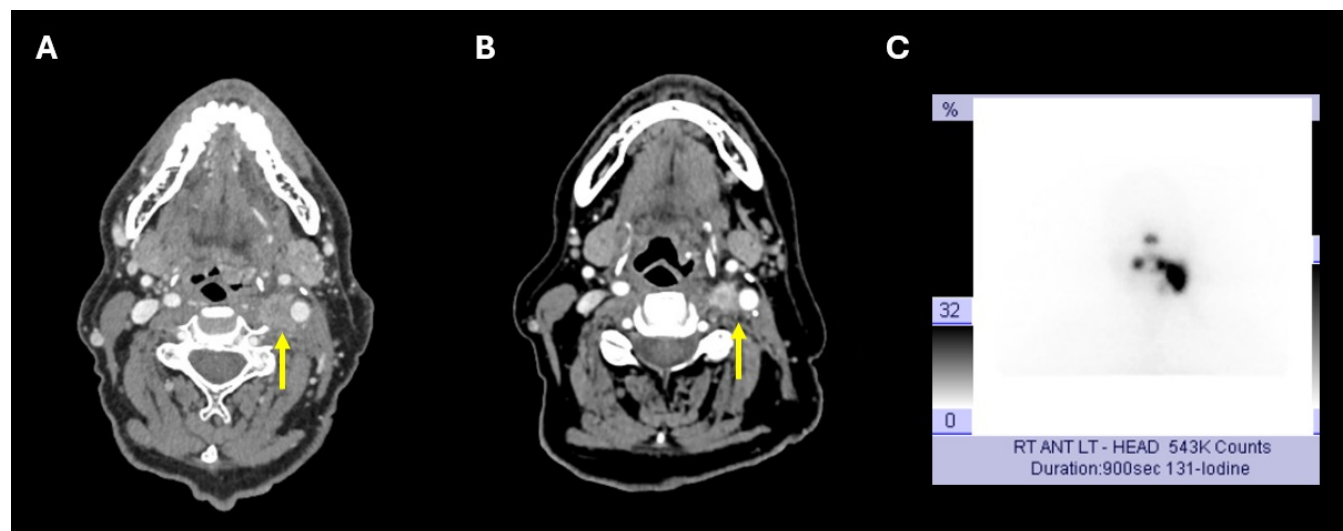
Lori J. Wirth, MD

Figure 1. Case 1 Patient CT 362



Arrows indicate the following findings: Panel A, left cervical adenopathy in May 2019; Panel B, lung metastasis in May 2019; Panel C, gastrohepatic adenopathy in May 2019; Panel D, left cervical adenopathy in July 2019; Panel E, lung metastasis in July 2019; Panel F, gastrohepatic adenopathy in July 2019.

Figure 2. Case 1 Patient CT and Post-RAI Whole-Body Scan 363



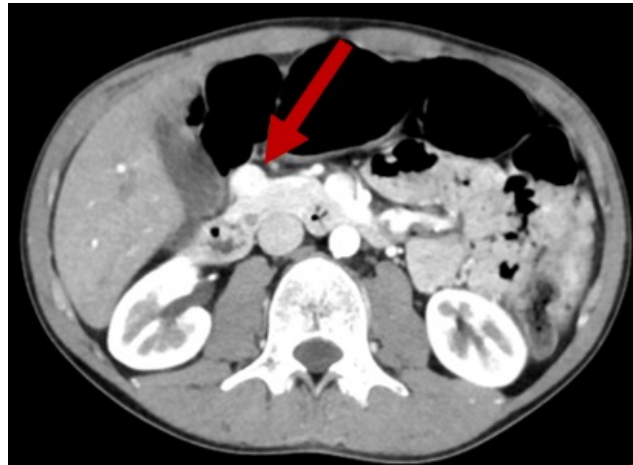
Panel A, left styloid parapharyngeal mass (arrow) in December 2023; Panel B, left styloid parapharyngeal mass (arrow) in April 2024; Panel C, Post-RAI whole-body scan in July 2024.

TUMOR BIOLOGY

Management of Duodenopancreatic Neuroendocrine Tumors in Patients With Multiple Endocrine Neoplasia Type 1

Thorvardur (Thor) R. Halfdanarson, MD, and Omair A. Shariq, MBBS, PhD

Figure 1. Case 1 Abdominal CT..... 378



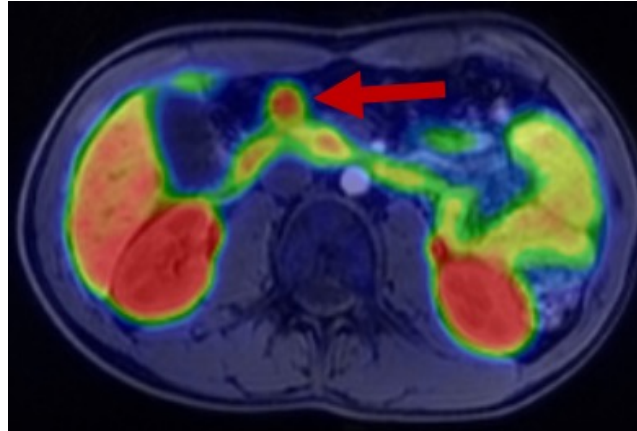
Abdominal CT (arterial phase) showing an enhancing mass in the head/neck region of the pancreas.

Figure 2. Case 1 Abdominal MRI..... 379



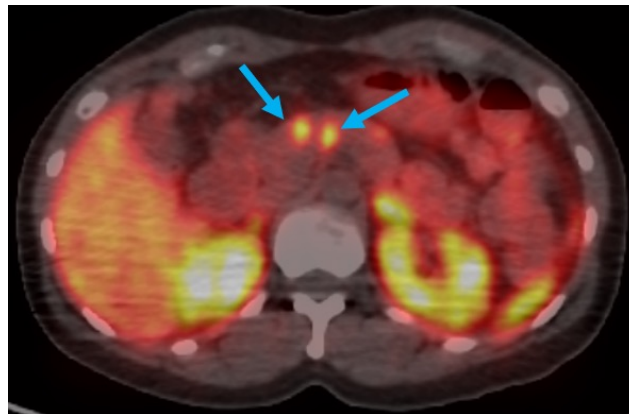
Abdominal MRI (arterial phase) showing an enhancing mass in the head/neck region of the pancreas.

Figure 3. Case 1 SSTR (^{68}Ga DOTATATE) PET-MRI 379



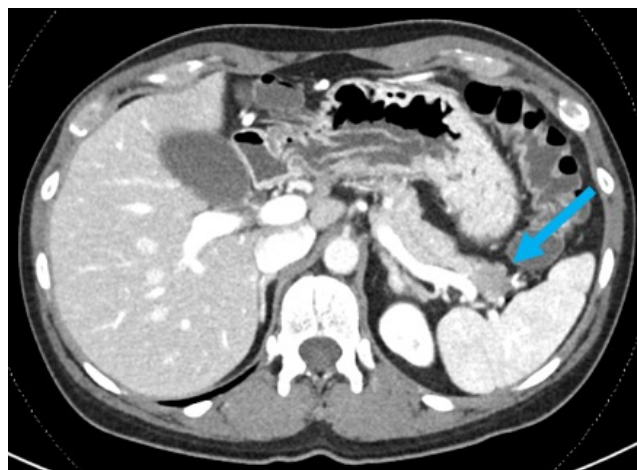
SSTR (^{68}Ga DOTATATE) PET-MRI showing an SSTR-avid mass.

Figure 4. Case 2 SSTR PET-CT 381



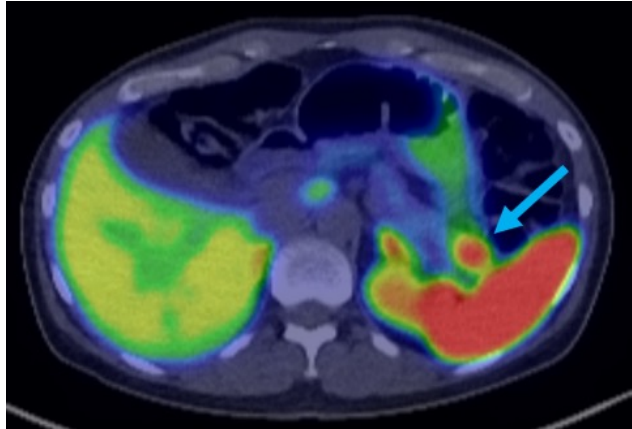
SSTR PET-CT showing 2 foci of avidity in the pancreatic body.

Figure 5. Case 2 CT of the Abdomen and Pelvis 381



CT of the abdomen and pelvis showing a pancreatic tail mass.

Figure 6. Case 2 SSTR PET-CT 382



SSTR PET-CT showing an SSTR-avid pancreatic tail mass.

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